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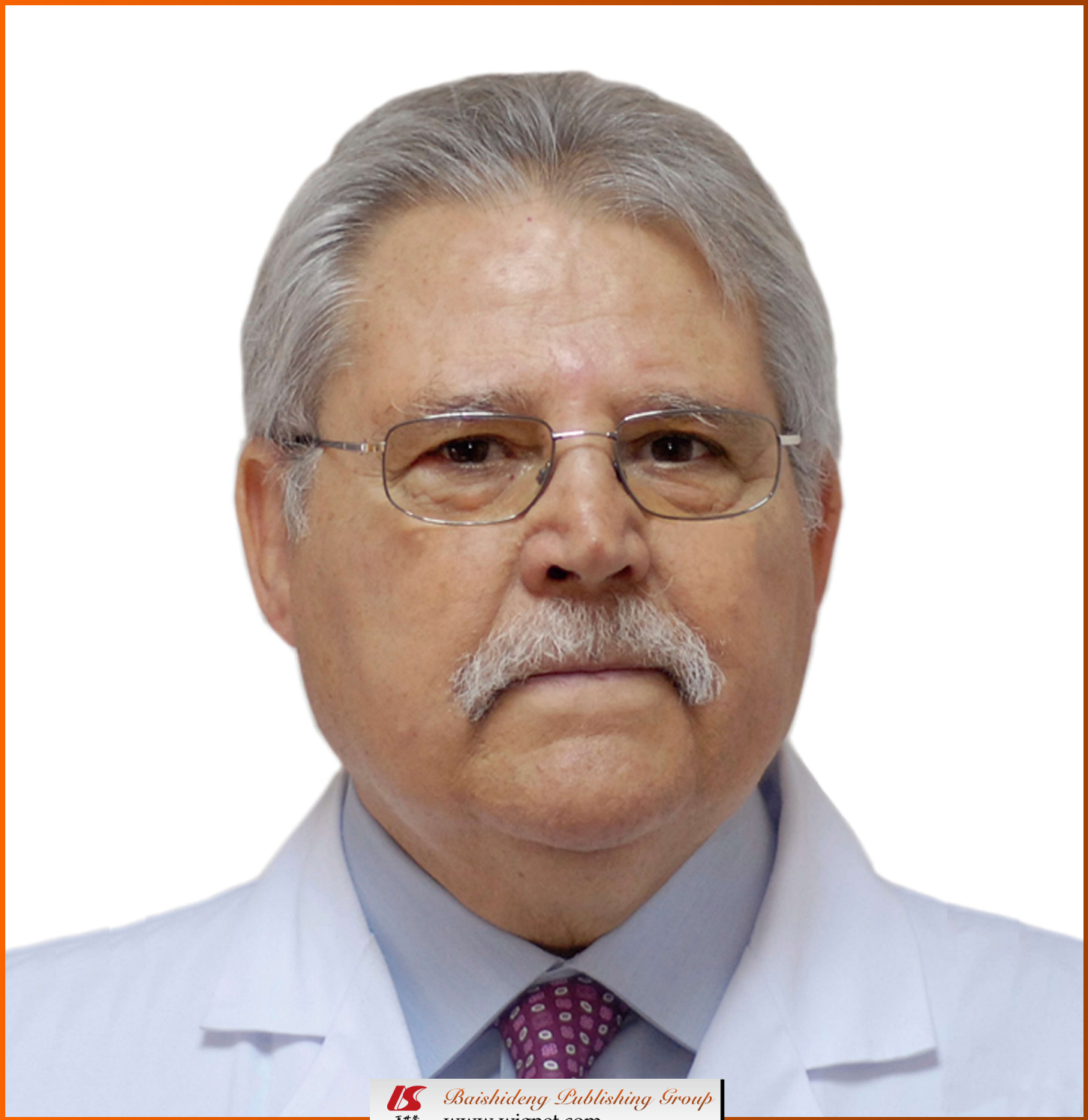

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EDITORIAL

Direct peroral cholangioscopy

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Abstract

Peroral cholangioscopy is an important tool for diagnosis and treatment of various biliary disorders. Peroral cholangioscopy can be performed by using a dedicated cholangioscope that is advanced through the accessory channel of a duodenoscope, or by direct insertion of a small-diameter endoscope into the bile duct. Direct peroral cholangioscopy refers to insertion of an ultraslim endoscope directly into the bile duct for visualization of the biliary mucosa and lumen. This approach provides a valuable and economic solution for diagnostic and therapeutic applications in the biliary tree. Compared to ductoscopy using a dedicated cholangioscope, the direct approach has several advantages and disadvantages. In this editorial, I discuss the advantages, disadvantages, and possible future developments pertaining to direct peroral cholangioscopy.

Key words: Cholangioscopy; Direct peroral cholangioscopy; Dedicated cholangioscopes

Core tip: Direct peroral cholangioscopy is a valuable and economic tool for diagnostic and therapeutic applications in the biliary tree. However, solutions are needed to make access to the biliary tree easier, and to improve the endoscope stability within the biliary tree for diagnostic and therapeutic maneuvers.

Parsi MA. Direct peroral cholangioscopy. *World J Gastrointest Endosc* 2014; 6(1): 1-5 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i1/1.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i1.1

METHODS OF PERORAL CHOLANGIOSCOPY

Peroral cholangioscopy has numerous applications in diagnosis and treatment of various biliary disorders[1]. Currently, peroral cholangioscopy can be performed by two different methods: (1) by using a dedicated cholangioscope and (2) by direct insertion of a small-diameter upper endoscope into the biliary tree (the direct method).

Peroral cholangioscopy using a dedicated cholangioscope

In this approach, a dedicated cholangioscope is advanced through the accessory channel of a duodenoscope and directed into the bile duct (Figure 1). A biliary sphincterotomy is usually necessary for advancement of the cholangioscope through the biliary sphincter. Although biliary cannulation can be achieved directly with the tip of the cholangioscope, most endoscopists prefer cannulation over a guidewire[2]. Once the scope is advanced to the target location, the guidewire is removed to enhance visualization and to permit use of the working channel. The duct is irrigated with sterile saline solution through the accessory channel of the cholangioscope for adequate visualization, followed by slow withdrawal of the scope, allowing systematic inspection of the ductal mucosa and lumen.

Direct peroral cholangioscopy

In direct peroral cholangioscopy, an ultraslim upper endoscope is inserted through the mouth and advanced to the duodenum. It is subsequently maneuvered across the biliary sphincter and into the bile duct for observation of the mucosa and the lumen of the bile duct (Figure 2). Maneuvering of the endoscope across the biliary sphincter requires presence of a sphincterotomy and in most cases performance of a balloon sphincteroplasty. Presence of a guidewire in the bile duct often allows a more proximal access, to the common hepatic duct. The guidewire is subsequently removed to better visualize the lumen and mucosa, to allow more freedom of movement at the tip of the endoscope and to make the accessory channel available for therapeutic measures if needed. The bile duct is irrigated with sterile saline solution through the accessory channel of the ultraslim endoscope followed by slow withdrawal of the endoscope allowing systematic inspection of the biliary tree. Sterile saline irrigation can be substituted with carbon dioxide (CO_2) insufflation. In a study involving 19 patients with suspected biliary disease, Ueki *et al*[3] reported superior image quality using CO_2 insufflation compared to saline irrigation. Another study involving 36 patients, however, reported that although the median time required to obtain a clear endoscopic image using CO_2 insufflation was significantly shorter than that required for saline irrigation, the quality of the endoscopic images obtained was similar in the majority of cases[4]. Air insufflation during direct cholangioscopy has been associated with serious adverse events and its use has been discouraged[5].

With the introduction of high-definition ultraslim upper endoscopes with narrow band imaging capability, direct peroral cholangioscopy has become more popular. The ultraslim upper endoscopes currently used for direct peroral cholangioscopy have an outer diameter of approximately 5 mm and an instrument channel with an inner diameter of approximately 2 mm[5].

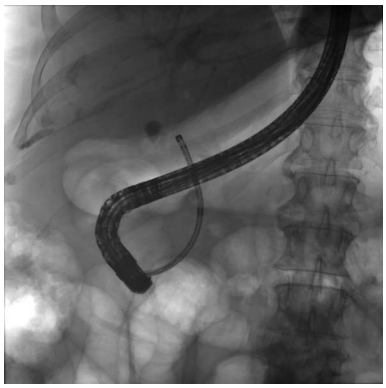

Figure 1 Cholangioscopy using a dedicated cholangioscope. In this approach, a dedicated cholangioscope is advanced through the accessory channel of a duodenoscope and directed into the bile duct.

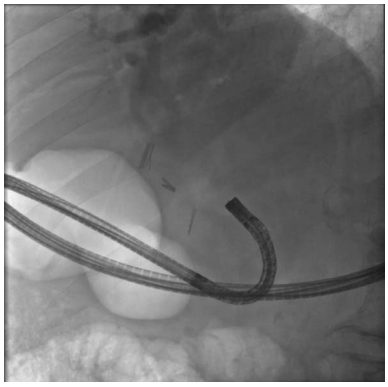

Figure 2 In direct peroral cholangioscopy, an ultraslim upper endoscope is inserted through the mouth and advanced to the duodenum. It is subsequently maneuvered across the biliary sphincter and into the bile duct for observation of the mucosa and the lumen of the bile duct.

ADVANTAGES OF DIRECT PERORAL CHOLANGIOSCOPY

Commercial availability

In cholangioscopy, whether direct or using a dedicated cholangioscope, the quality of the image is of utmost importance. Among dedicated cholangioscopes, only high-definition video cholangioscopes can offer the same image quality as the ultraslim upper endoscopes used in direct cholangioscopy. Dedicated high-definition video cholangioscopes are currently produced only as prototypes and thus not available for commercial use. Ultraslim upper endoscopes used for direct cholangioscopy, on the other hand, are widely available on a commercial basis.

Image quality

Currently, none of the commercially available dedicated cholangioscopes can offer high-definition images. High definition, refers to an increase in pixels (dots) received by the endoscope and displayed on the monitor to increase the detail of the surface being seen, enabling detection of smaller and more obscure lesions[6]. It also may allow for more detailed examination of lesions that may already have been seen in standard definition, although, with less detail. The new-generation of ultraslim upper endoscopes offer high-definition images allowing detailed examination of biliary mucosa and ductal lumen with subsequent increase in their diagnostic capability (Figure 3).

Operating expense

Currently-available dedicated cholangioscopes are expensive to use. The single-operator cholangioscopy systems have single-use components that have to be discarded after each case while the dual-operator systems are fragile, break easily and are in need of frequent repairs[1,2]. The expenses associated with direct cholangioscopy are far less compared to use of dedicated cholangioscopes.

Narrow band imaging capability

At present, commercially available dedicated cholangioscopes do not have narrow band imaging capability.

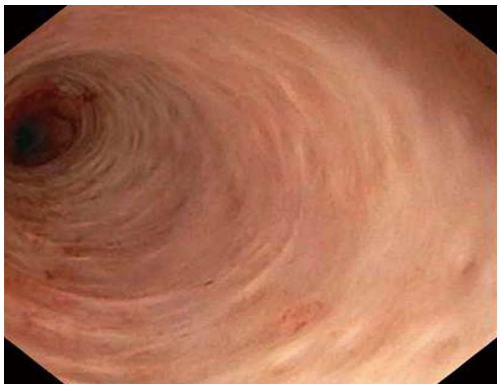

Figure 3 View of the bile duct lumen and mucosa by direct peroral cholangioscopy. Note the normal pit pattern.

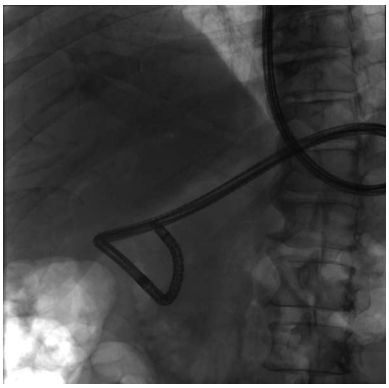

Figure 4 Fluoroscopic view of the ultraslim upper endoscope. Note looping of the endoscope in the stomach. Although the tip of the endoscope is well within the bile duct lumen, the endoscope cannot be further advanced to the more proximal ducts because of the looping.

Described by Gono and colleagues for the first time in 2004, narrow band imaging uses electronic processing of light in order to highlight particular components of an image[7,8]. The principle behind narrow band imaging technology is that the bandwidths of blue and green light are narrowed while the contribution of red light is negated out of the emitted light[8]. The narrowed bandwidths of green and blue light lead to superficial penetration of the mucosa accentuating the microvasculature pattern as hemoglobin has a peak absorption spectrum towards both these wave lengths[8]. Narrow band imaging can therefore improve visualization of the vascular pattern and aid in the diagnosis of various biliary disorders particularly indeterminate biliary strictures[2].

Size of accessory channel

The currently available ultraslim upper endoscopes have an accessory channel with an inner diameter of 2 mm, which is much larger than the accessory channel of the dedicated cholangioscopes measuring approximately 1.2 mm[2,5]. The larger size of the accessory channel allows easier passage of equipment such as biopsy forceps for tissue sampling or lithotripsy probes for fragmentation of difficult to remove biliary stones.

Operating a single endoscope

Compared to dedicated cholangioscopy which requires simultaneous operation of two endoscopes (the duodenoscope and the dedicated cholangioscope), direct cholangioscopy involves only a single endoscope that is manipulated into the lumen of the bile duct by a single endoscopist. Dealing with only one endoscope, avoids problems associated with simultaneous operation of multiple endoscopes such as coordination of movements.

Simultaneous irrigation, suction and therapeutic maneuvers

The ultraslim upper endoscope allows simultaneous irrigation, suction and therapeutic maneuvers. None of the currently available dedicated cholangioscopes have this capability.

DISADVANTAGES OF DIRECT PERORAL CHOLANGIOSCOPY

Larger outer diameter of the endoscope

The ultraslim upper endoscopes have an outer diameter of 5-6 mm, which is significantly larger than the diameter of most dedicated peroral cholangioscopes (3.0-3.5 mm). Direct cholangioscopy using the ultraslim upper endoscopes can therefore be performed only in patients with dilated bile ducts. In addition, the larger outer diameter requires generous sphincterotomy and sphincteroplasty for manipulation of the endoscope across the biliary sphincter.

Difficulty of insertion into the bile duct

The most profound disadvantage of direct peroral cholangioscopy is the difficulty associated with traversing the biliary sphincter to gain access to the bile duct. A high percentage of direct peroral cholangioscopy procedures, therefore, end up in failure. This difficulty of bile duct cannulation with an upper endoscope is mainly due to the looping of the ultraslim upper endoscope in the stomach or in the duodenum (Figure 4). There are therefore multiple published reports in the endoscopic literature with innovative suggestions on how to achieve this task. Introduction of the endoscope over a guidewire, through a regular overtube, or with the help of a double-balloon overtube are some of the suggestions[9-12]. However, despite use of these accessories, failure rate still remains high[13].

Lack of stability inside the bile duct

Another disadvantage of direct cholangioscopy is the instability of the ultraslim upper endoscope once it is inside the bile duct. This instability makes it difficult to perform diagnostic or therapeutic procedures such as

Table 1 Comparison of direct and dedicated cholangioscopy

	Direct cholangioscopy	Dedicated high-definition cholangioscopy
Commercial availability of the endoscope	Yes	No (prototypes)
Operating expense	Low	High
Image quality	Excellent	Excellent
Narrow band imaging capability	Yes	Yes
Required number of operators	One	Two
Irrigation capability	Yes	Limited
Suctioning capability	Yes	Limited
Fragility	No	Yes
Size of accessory channel	2 mm	1.2 mm
Insertion into the bile duct	Difficult	Easy
Stability inside the bile duct	Unstable	Stable
Access to proximal ducts	No	Yes

obtaining biopsies of lesions or lithotripsy of difficult to remove biliary stones. Endoscope instability can also lead to loss of access and prolongation of the procedure.

Lack of access to proximal ducts

In direct peroral cholangioscopy, access to the more proximal ducts is often not possible. Usually direct cholangioscopy can only visualize the ducts distal to the confluence of the right and left hepatic ducts. The right and left hepatic ducts and their branches are for the most part inaccessible for direct peroral cholangioscopy, limiting its use in only the most distal parts of the biliary tract[5].

FUTURE DIRECTIONS

Despite its many advantages, direct peroral cholangioscopy is rarely performed in nonacademic settings, mostly because of the difficult and time-consuming task of bile duct cannulation with an upper endoscope. Different variations of inflatable balloons used as an anchor within the biliary tree have been introduced for easier access[5,14]. Although these devices perform well for allowing access to the bile duct for assessment and therapy of disorders of the distal biliary system, it is often difficult to maneuver the endoscope and gain access to the ducts proximal to the bifurcation after deflation and removal of the anchoring balloon. Devices, such as overtubes, that can allow more proximal access while improving the stability of the endoscope are needed.

Currently, direct peroral cholangioscopy can only be performed in patients with dilated biliary tree. Ultraslim upper endoscopes with smaller outer diameter but preserved stiffness designed for direct peroral cholangioscopy will be a welcome addition to the existent array of endoscopes.

Finally, accessory equipment designed for use in direct peroral cholangioscopy can further improve the utility of this procedure.

CONCLUSION

Peroral cholangioscopy is an important tool for diagnosis and treatment of various biliary disorders. Peroral cholangioscopy can be performed by using a dedicated cholangioscope or by direct insertion of an ultraslim endoscope into the bile duct (direct peroral cholangioscopy). Compared to ductoscopy using a dedicated cholangioscope, the direct approach has several advantages and disadvantages (Table 1). The direct approach provides a valuable and economic solution for diagnostic and therapeutic applications in the biliary tree. However, solutions are needed to make access to the biliary tree easier, and to improve the endoscope stability within the biliary tree for diagnostic and therapeutic maneuvers.

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EDITORIAL

Virtual reality simulators for gastrointestinal endoscopy training

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Abstract

The use of simulators as educational tools for medical procedures is spreading rapidly and many efforts have been made for their implementation in gastrointestinal endoscopy training. Endoscopy simulation training has been suggested for ascertaining patient safety while positively influencing the trainees' learning curve. Virtual simulators are the most promising tool among all available types of simulators. These integrated modalities offer a human-like endoscopy experience by combining virtual images of the gastrointestinal tract and haptic realism with using a customized endoscope. From their first steps in the 1980s until today, research involving virtual endoscopic simulators can be divided in two categories: investigation of the impact of virtual simulator training in acquiring endoscopy skills and measuring competence. Emphasis should also be given to the financial impact of their implementation in endoscopy, including the cost of these state-of-the-art simulators and the potential economic benefits from their usage. Advances in technology will contribute to the upgrade of existing models and the development of new ones; while further research should be carried out to discover new fields of application.

Key words: Virtual endoscopic simulators; GI Mentor; Accutouch endoscopy simulator; Olympus Endo TS-1; Endoscopy training

Core tip: Virtual endoscopic simulators have a great potential in endoscopy training. There are currently two virtual simulators available to purchase as well as others available for non-commercial use. The use of virtual simulators in endoscopy boosts training procedure for upper and lower gastrointestinal endoscopy; the benefits being more prominent in novice trainees. More data are needed to document their position in endoscopic retrograde cholangiopancreatography and endoscopic ultrasound training. Available simulators should not be considered a tool for assessing the skills of endoscopists. The main disadvantage of virtual simulators is their high cost.

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INTRODUCTION

The aim of endoscopy is to achieve the best diagnostic-therapeutic result while minimizing the risks of the patient. Acquiring skills to perform endoscopy needs experience and time and depends on the ability of the trainee,

the feedback given by an experienced supervisor and the method of endoscopy training. Traditionally, novice residents commence their training by performing endoscopies on patients, which might result in prolonged procedure time[1] and abdominal pain and discomfort for the patient[2] due to lack of experience. In the era of higher endoscopy costs and increasing demand for advanced invasive procedures that minimize training opportunities[3], endoscopy simulation has been pointed out as a method of maintaining patient safety through reducing endoscopy errors[4-6] and achieving better and faster training results. Over the last decades, the use of endoscopy simulators has been spreading rapidly and an increasing number of medical centers in various countries worldwide have already incorporated them in endoscopy training.

ENDOSCOPY SIMULATORS

The first attempts of developing endoscopy simulators were found at the end of the 1960s with the creation of the first mechanical models[7]. Mechanical simulators have given their position to other more useful and realistic types of simulators, such as live animal models, *ex-vivo* simulators and virtual simulators. Although animal models are considered to offer the most human-like endoscopy experience, they are not widely used due to ethical concerns, the requirement for the presence of experienced staff, unavailability of necessary equipment and cost[8]. *Ex-vivo* simulators, which engage plastic materials with explanted animal organs are relatively cheap devices useful for scenario based training[9]. On the other hand, the need for tissue replacement increases preparation time, raises the cost and limits the trainee's access to training sessions[9]. Virtual (computerized) endoscopy simulators are presented as the most promising tool in endoscopy training. First developed in the 1980s[10,11], their use is spreading throughout the world and computer evolution aids the rapid improvement of these high-tech modalities. In this editorial, we will focus on virtual simulators, discussing their role in endoscopy training by reviewing the available literature.

VIRTUAL ENDOSCOPY SIMULATORS

Virtual endoscopy simulators are integrated systems that consist of mechanical parts and software. They run a computer program that simulates the procedure of endoscopy using endoscopic images of the gastrointestinal tract while the trainee handles an endoscope attached to a processor that gives a signal to a monitor. The moves of the endoscope interact with the monitor image, offering the user a virtual environment for practicing theoretical and practical knowledge under various conditions[12]. There are currently two virtual simulators in the market: GI Mentor (Simbionix, Cleveland, United States) and Accutouch Simulator, recently renamed as CAE EndoVR Simulator (CAE Healthcare, Montreal, Quebec, Canada)[13-15]. There are also simulators available for non-commercial use, such as the Endo TS-1 simulator (Olympus Keymed, Essex, United Kingdom), the construct validity of which has been tested in several trials.

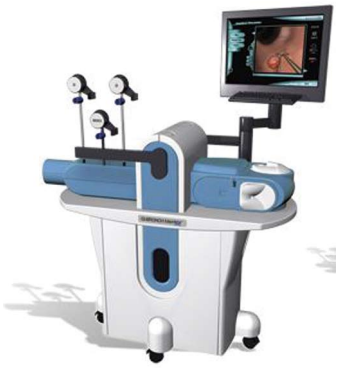

Figure 1 The GI Mentor II simulator (Simbionix, Cleveland, United States), photo provided courtesy of Simbionix.

GI Mentor

Simbionix, a Cleveland, Ohio, United States headquartered company with an Israeli based research unit, produced the virtual simulator that offers the widest variety of tasks available. Suitable for upper and lower endoscopy training, GI Mentor provides a large library of modules from basic endoscopic skills and simple clinical procedures to complicated situations such as emergency gastric bleeding. There are also modules for endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) training. The simulation program includes features like a pain indicator and scope locator and trainees also have the opportunity to practice on virtual patient cases based on actual medical data[16] (Figure 1).

Accutouch endoscopy simulator

Although the company recently changed the name of the simulator, we will keep the old name throughout the manuscript because it appears as "Accutouch" in the available literature. The redesigned in 2012 simulator of CAE Healthcare (Canada) provides the user with a new, more realistic haptic sense of endoscopy. Modules of esophagogastroduodenoscopy (EGD), colonoscopy and endoscopic retrograde cholangiopancreatography (ERCP) are available and the trainee can also acquire skills in polypectomy, biopsy and hemostasis[17]. CAE's simulator offers a complete endoscopy experience by combining the endoscopy procedure with the background of a virtual patient. Endoscopy starts with the patient's history and various parameters change during endoscopy, such as vital signs and patient response to pain and discomfort. The trainee is also assigned to achieve the ideal virtual sedation without reducing the patient's oxygen saturation[18] (Figure 2).

Olympus colonoscopy simulator (Endo TS-1)

The Endo TS-1 (Olympus Keymed, United Kingdom) is

Figure 2 The CAE EndoVR (previously Accutouch) simulator (CAE Healthcare, Montreal, Canada), © 2013 CAE. Photo provided courtesy of CAE Healthcare.

a second generation virtual reality simulator that provides real-time movements of the colonoscope[19]. An Olympus CF180L endoscope is customized for the needs of the simulator and gives the user a realistic colonoscopy-like haptic sense by simulating the moves of the endoscope and the patient[20]. Olympus' Scope Guide that provides a 3-dimensional image of the position and shape of the endoscope within the colon was used as a pattern for Endo TS-1 and the luminal view is accompanied by a training tutorial[20]. The software is currently being updated and more complex procedures, like polypectomy, will be added[20].

USING VIRTUAL ENDOSCOPY SIMULATORS

From the first efforts of creating virtual endoscopy simulators to now, the positioning of these modalities regarding endoscopy training is still questioned. Numerous studies tried to investigate the improvement of endoscopy skills of trainees with various experience in endoscopy after receiving sessions of virtual endoscopy training. Other studies focused on using virtual simulators for the evaluation of acquired skills. Undoubtedly, use expansion of these high tech computer based machines depends on giving answers to these important issues.

Training

The significant acceleration of training procedure to the threshold that trainees are considered to have acquired sufficient skill is the most important condition for the positive validation of a simulator[21,22]. Although modern virtual endoscopy simulators offer a large variety of modules, trials reviewed herein examine only the effect of virtual endoscopic training in upper gastrointestinal endoscopy, colonoscopy and flexible sigmoidoscopy. The results of the major trials that examined the influence of virtual endoscopy simulators in gastrointestinal endoscopy training of novice trainees are shown in Table 1.

Regarding upper gastrointestinal endoscopy, training with the GI Mentor simulator in combination with a mechanical and an *ex-vivo* simulator seems to positively influence the learning curve of novice endoscopists when combined with clinical training, while independent simulator training appears to be insufficient[23]. Data reviewed from a Medical University of Vienna study indicate that trainees who underwent training sessions with a virtual endoscopy simulator before conventional training benefited in their first ten endoscopies on patients regarding procedure completion time and technical accuracy (as rated by experts) in comparison to their non-simulator trained fellows. A statistically significant difference in gastroscopy duration was still observable after 60 endoscopic examinations[24]. On the other hand, missed diagnosis of pathological findings, evaluated by blinded experts, was not significantly different between the two groups[24].

Three randomized, blinded, controlled trials have demonstrated the positive impact of three different virtual endoscopy simulators on the performance of novice colonoscopists. The first study, performed in Karolinska Hospital, Sweden, proved a significant increase of colonoscopy completion rate and reduction of both procedure time and patient discomfort in trainees who had already achieved a predetermined performance in the Accutouch simulator compared with controls[25]. In the second multicenter trial, the influence of GI Mentor simulator pre-training was investigated. The results showed that the pre-trained residents achieved higher competency scores than their control trainees during their first 100 cases; the difference in performance was even more prominent in their first 80 colonoscopies[26]. A third multinational European trial proved that novice trainees trained with the Olympus virtual simulator received similar rates by blinded experts in three live colonoscopy cases in comparison to others who underwent traditional training only. However, they achieved better results in simulator metrics in three virtual simulator cases than their fellows trained on patients[27].

Furthermore, one study demonstrated that skills acquired after sessions of colonoscopy training with virtual endoscopy simulators seem to be maintained for several months after the end of training[28]. The presence of a supervisor also boosts the training procedure as trainees complete the colonoscopy simulation and reach simulator proficiency levels faster than individual training[29]. Finally, intensive hands-on colonoscopy courses using computer simulator and live case teaching positively influence trainees' skills measured by a computer simulator and by a clinical index, while results are maintained during a 9 mo follow-up period[30].

The use of sigmoidoscopy virtual simulators was investigated in two trials. The results of a prospective randomized trial were not promising since trainees who were trained using virtual endoscopy simulators exclusively experienced more technical difficulties regarding initial endoscope insertion, negotiation of the rectosigmoid junction and ability to perform retroflexion, while their procedure completion rate was significantly lower than that of controls[3]. Another study demonstrated that a 3 h

Table 1 Evaluation of virtual simulators for the training of novice endoscopists

Ref.	Simulator	Procedure	Groups	Outcome measurement	Result
Ende *et al*[23]	GI Mentor (plus a mechanical and an *ex-vivo* simulator)	Gastroscopy	Clinical plus simulator training Clinical training only Simulator training only	Skills evaluation score Time (s) to pass pylorus	Median score: 7 *vs* 6 *vs* 5 (P = NS) 183 ± 65 *vs* 207 ± 61 *vs* 247 ± 66 (P = NS)
Ferlitsch *et al*[24]	GI Mentor	Gastroscopy	Simulator training before conventional training Conventional training	Time (s) to reach duodenum Percentage of unaided examinations (after 10 endoscopies)	239 *vs* 310 (P < 0.000) 85% *vs* 72% (P < 0.01)
Ahlberg *et al*[25]	Accutouch simulator	Colonoscopy	Simulator group Control group	Cecum reached during the first 10 colonoscopies Time (min) to reach cecum Patient discomfort (estimated probability in group 2)	52% *vs* 19% (P = 0.0011) 30 *vs* 40 (P = 0.037) 2.27 (95%CI: 1.14-4.76)
Cohen *et al*[26]	GI Mentor	Colonoscopy	Simulator group Control group	Competency after 100 cases Number of cases for reaching competency	Higher in group 1 (P < 0.0001) 160 in both groups (P = NS)
Haycock *et al*[27]	Olympus simulator	Colonoscopy	Simulator group On patient trained group	Live colonoscopy cases Completion rates Time taken Virtual simulator cases Cecum intubation Time (s) to cecum intubation	11% *vs* 7% (P = NS) 20 min *vs* 20 min (P = NS) 95% *vs* 70% (P < 0.01) 407 *vs* 743 (P < 0.01)
Gerson *et al*[3]	Accutouch simulator	Sigmoidoscopy	Virtual simulator training (without on-patient training) On patient training group	Time (min) to complete the live case Live cases that trainees completed independently	24 *vs* 24 (P = NS) 29% *vs* 72% (P < 0.001)
Sedlack *et al*[31]	Accutouch simulator	Sigmoidoscopy	Simulator group Control group	Patient discomfort score (1-10) Competence score to perform endoscopy independently (1-10)	1.3 *vs* 4 (P < 0.01) 2.8 *vs* 8 (P = NS)

NS: Not significant.

simulator pre-training course did not show a measurable effect in the graded skills of identification of pathology and safe scope insertion of novice trainees performing sigmoidoscopy. However, the patients experienced less discomfort[31].

There is limited information regarding the usefulness of virtual simulators in ERCP training. In two United States surveys in which ERCP virtual endoscopy simulators were evaluated compared to other modes (a mechanical simulator in the first study, an *ex-vivo* simulator and a live porcine model in the second), virtual simulators received lower scores in terms of realism and usefulness but they were ranked as more user friendly[32,33]. In another United States study, novice and expert endoscopists positively evaluated graphics and haptic realism of the ERCP module of GI Mentor and the vast majority of them claimed that it should be considered a useful ERCP training tool[34].

Finally, there are no data about GI Mentor's EUS mode contribution in trainees' learning curve. Kefalides *et al*[35] tested this EUS simulator mode and claimed that improvement is needed before being used as training tool. At the same time, eight EUS experts gave EUS Mentor mode the highest score among a mechanical simulator, an *ex-vivo* simulator and a live pig model in terms of usefulness and realism but expressed a negative view about the virtual simulator's EUS-FNA training mode[36].

Evaluation of endoscopic skills

The success of endoscopy depends on a number of factors, including among others, the endoscopist's technique, patient's condition and tolerance and the quality of equipment. As a result, it is difficult to assess endoscopic skills and there is no widely accepted scale for measuring competence. For a reliable evaluation of the training process, virtual endoscopy simulators must correlate simulator based benchmarks with clinical skills[37] and simulators' competitiveness scores with accepted clinical metrics[38].

The validation of the Olympus virtual simulator to evaluate colonoscopy skills has been tested in two different trials demonstrating promising results. In one trial that included participants with no endoscopy experience, trainees with median experience and experts showed a significant reduction of simulator procedure time and better scores in parameters measuring technique, like the number and size of passed sigmoid loops and use of variable stiffness function that depended on user's experience[20]. Another trial that included novices and experts demonstrated that experts achieved higher scores in colonoscopy competence measured by an Olympus simulator scale but the difference was not statistically significant[39].

Surveys involving GI Mentor as a skills assessment tool have shown contradictory results. Two studies, both dividing participants into novices, medium-experienced and expert endoscopists, have shown significant differences between novices and the other groups regarding virtual colonoscopy completion time and other parameters such as the percentage of lumen surface examined. Differences though were less prominent after the users had reached certain endoscopic experience[40,41]. A third

trial demonstrated that GI Mentor colonoscopy simulator modules with a higher level of complexity were more suitable to distinguish endoscopists with different experience[42]. On the other hand two other surveys raised doubts about the reliability of GI Mentor to evaluate colonoscopy skills. A University of Pennsylvania, United States trial showed that the virtual simulator was unable to differentiate between novices and experts, not only in colonoscopy modules but also in upper gastrointestinal endoscopy modules[43], while a Cleveland, United States study displayed a wide range of scores in virtual colonoscopies performed by experts, claiming that an upgrade is needed for simulators to be considered accurate tools for measuring endoscopic skills[44].

The ability of the GI Mentor ERCP module to discriminate between novices and experts was tested in a US study. The combination of results in two simulated cases proved a statistically significant difference between the two groups but the study sample size was small and only one institution was involved[34].

The construct validity of the Accutouch sigmoidoscopy simulator has been tested in two trials. The simulator discriminated between groups with different sigmoidoscopy experience but results from the simulator metrics were not statistically significant in one of the two studies where experts and senior trainees were compared[45,46].

Finally, an attempt for creating a universal scale for measuring competence using virtual simulators was made in a multicenter Canadian trial. The researchers developed the "Global Assessment of Gastrointestinal Endoscopic Skills" for upper gastrointestinal endoscopy and colonoscopy, demonstrating a statistically significant difference between the scores of novices and experts[47].

FINANCIAL IMPACT

The two virtual endoscopy simulators currently available in the market are quite expensive. The cost of GI Mentor starts from $64500 (gastroscopy and colonoscopy modes) but the purchase of more complicated modules, such as those available for ERCP and EUS training, can raise the cost up to $114000[9]. As far as the Accutouch simulator is concerned, upper and lower gastrointestinal endoscopy packages can be purchased separately. The cost of the upper gastrointestinal endoscopy package is $46750 (bleeding mode upgrade adds $19000 to the cost), while the lower gastrointestinal endoscopy package is available at $74750. The addition of advanced modules, like the ERCP module and colonoscopy biopsy module, increases the cost from $7175-8650 for each separate purchase[9]. This high cost is the main reason that precludes the widespread of these modalities in countries where the total number of endoscopy trainees does not justify the cost or current fiscal austerity measures impose tremendous cut in state public health spending[48].

Their main financial advantage in comparison to other types of simulators, like *ex-vivo* and animal models, is that after installation, the expenses are minimized. The presence of a supervisor in a virtual endoscopy training procedure is not cost effective according to a University of Alabama study[49]. The concept of mobile virtual endoscopy simulators, being shared by more than one institutions, proved successful[50] and collaborative use may reduce the cost of their use in the future. Use of virtual endoscopy simulators though seems to also have a positive influence in health economics by reducing procedure time related to trainee involvement in endoscopy[1] and by limiting potential procedural complications and incorrect diagnosis[51]. Further research should be carried out in order to quantify the profit from their use.

CONCLUSION

Virtual endoscopy simulators use at the early stages of endoscopy training has considerable impact in the performance of novice endoscopists, not only in gastroscopy but also in colonoscopy. The benefit of their use for trainees who have acquired certain experience appears to be limited, while more data is needed to document their position in ERCP and EUS training. Despite the efforts for developing virtual simulators as tools for measuring endoscopic skills, the available modalities should not be considered as an objective means for validating the competitiveness of endoscopists. The main disadvantage of these computer-based simulators is their notably high price. The concept of mobile simulators and the purchase of basic modules of virtual simulators could be a solution for reducing cost. Rapid improvement in software and hardware technology promises even more realistic simulators and replacement of the first stages of conventional training with simulator training at a reasonable and affordable cost is the developers' challenge for the future.

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ORIGINAL ARTICLE

Intraductal endoscopic radiofrequency ablation for the treatment of hilar non-resectable malignant bile duct obstruction

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Abstract

AIM: To evaluate the safety and technical success of endoscopic radiofrequency ablation (RFA) for palliative treatment of malignant hilar bile duct obstruction.

METHODS: In this study, a recently CE and FDA-approved endoscopic RFA catheter was first tested in an *ex vivo* pig liver model to study the effect of electrosurgical variables on the extent of the area of induced necrosis. Subsequently, a retrospective analysis was conducted of all patients treated with endoscopic RFA for malignant biliary obstruction at our center between February 2012 and April 2013. All patients received an additional plastic stent implantation into the biliary tree following RFA.

RESULTS: In the pig model, ablation time of 60-90 seconds using the bipolar soft coagulation mode at 8-10 watts with an effect of 8 was found to be the most feasible setting. Twelve patients (5 females, 7 males; mean age, 70 years) underwent 19 endoscopic RFA (range, 1-5) sessions. Deployment of RFA was successful in all patients. Systemic chemotherapy was administered in four patients. We observed biliary bleeding 4-6 wk after the intervention in three cases and two of these patients died: in one patient, spontaneous hemobilia occurred, whereas bleeding started during stent extraction in the other. In the third patient, bleeding was stopped by insertion of a non-covered self-expanding metal stent. Another three patients developed cholangitis during follow-up. Seven patients died during follow-up and median survival was 6.4 mo (95%CI: 0.05-12.7) from the time of the first RFA.

CONCLUSION: Endoscopic RFA is an easy to perform and technically highly successful procedure. However, hemobilia possibly associated with RFA occurred in three of our patients. Therefore, larger prospective studies are needed to further evaluate the safety and efficacy of this promising new method.

Key words: Radiofrequency ablation; Endoscopic retrograde cholangiopancreatography; Endoscopy; Cholangiography; Bile duct cancer; Cholangiocarcinoma

Core tip: Radiofrequency ablation (RFA) is a promising tool for the treatment of patients with perihilar and intrahepatic bile duct cancer. While RFA is easy to perform and technical success rates are high, the outcome of patients remains unclear. Therefore, the long-term efficacy of this treatment approach needs to be studied in randomized trials.

Tal AO, Vermehren J, Friedrich-Rust M, Bojunga J, Sarrazin C, Zeuzem S, Trojan J, Albert JG. Intraductal endoscopic radiofrequency ablation for the treatment of hilar non-resectable malignant bile duct obstruction. *World J Gastrointest Endosc* 2014; 6(1): 13-19 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i1/13.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i1.13

INTRODUCTION

Hilar cholangiocarcinoma (CCA) accounts for about 70% of biliary tumors[1] and is not amenable to curative surgical resection in more than two thirds of cases at the time of diagnosis[1]. Palliative chemotherapy may increase median survival when a combination of chemotherapeutic agents is used[2]. In addition, endoscopic insertion of plastic endoprostheses or self-expanding metal stents (SEMS) plays an important role in the palliative treatment of biliary tract cancer[3,4].

Randomized controlled trials have indicated that endoscopic local ablation of intraductal CCAs by use of photodynamic therapy (PDT) significantly improves survival in non-resectable tumors[5,6] and these findings are also supported by non-randomized studies[7-10]. However, PDT is complex and expensive, requiring highly specialized equipment. Recently, ablation of intraductal tumors has been simplified by the introduction of a radiofrequency ablation (RFA) probe, the Habib EndoHBP probe (EMcision UK, London, United Kingdom) that is inserted through the working channel of a side-viewing endoscope during endoscopic retrograde cholangiopancreatography (ERCP) into the extra- and/or intra-hepatic biliary tract[11].

To date, few data exist on the clinical applicability of this new device. We therefore performed a retrospective analysis of all consecutive patients treated with endoscopic RFA for malignant biliary obstruction at our center, with a special emphasis on technical success rates, safety and patient survival.

MATERIALS AND METHODS

Pre-clinical study

Before the start of RFA treatments in patients, we performed an experimental pre-clinical study in an *ex-vivo* pig liver model to investigate the effect of electrosurgical variables on the extent of the area of RFA-induced necrosis. All procedures were performed using a RFA probe for bipolar cautery intended for use in endoscopic surgical procedures as described below (Habib EndoHPB; EMcision UK, London, United Kingdom; Figure 1).

In total, five consecutive freshly resected livers from adult pigs were obtained. All experiments were started within eight hours after the pigs had been euthanized and were performed at room temperature. The probe was advanced into the center of the liver over a guidewire and radiofrequency ablation was performed using different variations of power (watts), mode (effect) and ablation time. Ablations were performed with each technical setting three times in a row and the probe was inserted at least three centimeters apart from other ablation sites. Immediately after each application, the liver was cut along the guidewire with a scalpel to identify the ablation extent. The maximum diameter and length of the ablated area was measured separately for each application (Figure 2).

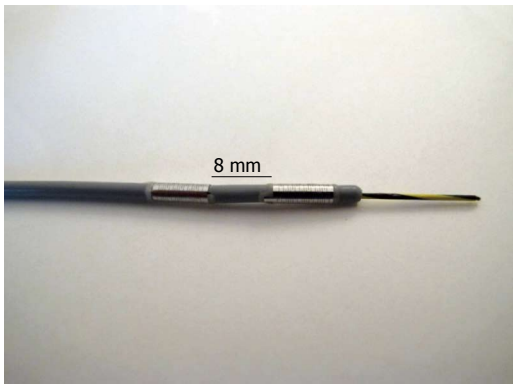

Figure 1 The radiofrequency ablation probe Habib EndoHPB (EMcision United Kingdom, London, United Kingdom) features two ring electrodes at the tip that are 8 mm apart. The probe is designed to perform bipolar cautery in endoscopic surgical procedures.

Clinical study

RFA was performed in patients with unresectable malignant biliary duct obstruction after the most feasible (8 to 10 watts, effect 8, 60-90 s) probe settings for optimal radiofrequency ablation had been identified in the preclinical study at our center starting in February 2012. All patients treated with endoscopic RFA for malignancy of an intrahepatic or perihilar bile duct were eligible for inclusion in this study and the study protocol was approved by the ethics committee of the Medical School of the University of Frankfurt, Germany. None of the patients had been eligible for curative surgery or had undergone a previous explorative laparotomy due to locally advanced disease or comorbidities. However, all patients reported symptoms such as painless jaundice or weight loss. Histological diagnoses were obtained by percutaneous needle biopsy or intraductal endoscopically operated biopsy during ERCP. All endoscopic RFA procedures were ascertained in an interdisciplinary conference of consultant physicians from the departments of surgery, gastroenterology and medical oncology and treatment recommendations were given in consent.

All endoscopic procedures (ERCP) were performed by an experienced pancreatobiliary endoscopist under standard operating conditions with a commercially available duodenoscope (TJF-160 VR or TJF Q180V, Olympus medical, Tokyo, Japan). Previously inserted plastic endoprostheses were removed before cholangiography, which were then used to confirm biliary length, diameter and localization of the tumor stenosis.

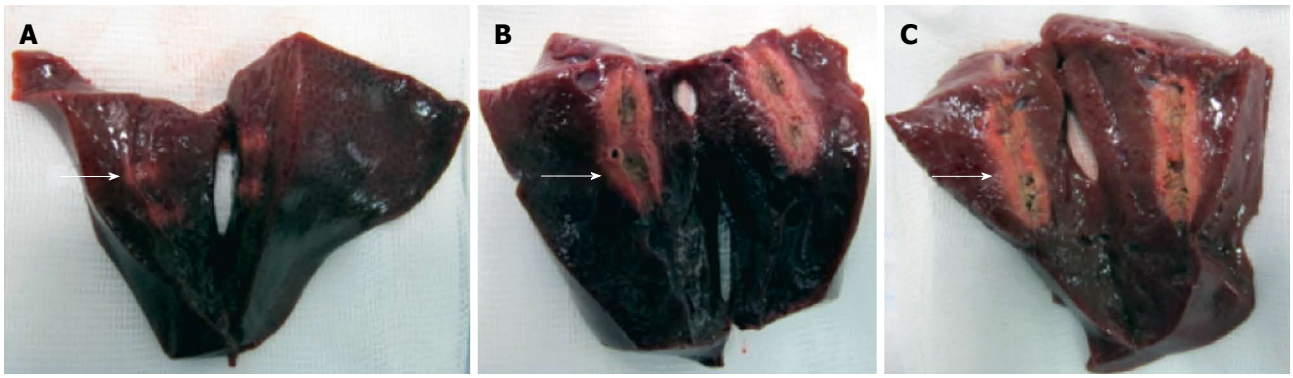

Figure 2 Exemplary results from the *ex vivo* pig liver model. From left to right, higher watt variables were used. Necrotic areas are marked by a arrow.

For endoscopic RFA, a recently FDA-approved and CE-certified[12] catheter was used. This probe (Habib EndoHPB; EMcision UK, London, United Kingdom) features two ring electrodes at the tip, lying 8 mm apart from each other (Figure 1). The catheter measures 8 French (2.6 mm) in diameter and 1.8 m in length. The RFA catheter can be connected to a bipolar electrosurgical generator to produce a cylindrical necrosis around the ring electrodes. The extent of the necrotic area depends on the mode of the electrosurgical generator, the power and ablation time. For the present study, the VIO 200D generator (Erbe Elektromedizin, Tübingen, Germany) with the "bipolar soft coagulation" mode, effect 8, 8 to 10 watts, for 90 s for treatment of the patients. Power was applied with 8 watts for the left or right intrahepatic biliary ducts and 10 watts for the subhilar section of the common hepatic or common bile duct, respectively. The RFA catheter was placed under fluoroscopic visualization of the biliary system after having visualized the tumor stenosis by injecting contrast medium (Iomeprol, Imeron® 300M, Bracco Imaging Deutschland, Konstanz, Germany) into the bile duct system *via* a standard ERCP probe. Positioning of the RFA catheter was performed exactly within the tumor stricture by using a guidewire. In cases of a stenosis more than 15 mm in length, repeated applications of RFA were carefully applied without overlapping the treated segments (1-4 applications per intervention). Thus, the RFA catheter was positioned into the right and/or the left intrahepatic bile ducts and we aimed to treat all segments involved in each specific tumor-dependent setting (Figure 1). After RFA treatment, plastic endoprostheses (Gastrosoft; Optimed, Ettlingen, Germany) were inserted according to standard protocols. The technical success of RFA was defined as positioning the RFA catheter at the region of interest and applying coagulation current as intended with consecutive successful insertion of an endoprosthesis.

Statistical analysis

The clinical part of this study is a retrospective cohort study. Data were analyzed from patients who underwent endoscopic RFA between February 2012 and April 2013 at our study center. The primary endpoint was the technical feasibility of endoscopic RFA. Secondary outcome measures included peri-interventional complications and overall survival.

Descriptive statistics are shown as mean ± SD or median and range, as appropriate. Survival was assessed using Kaplan-Meier statistics. All analyses were performed using the SPSS statistics software package for Mac (Version 20.0; IBM, Somers, NY, United States).

RESULTS

Pre-clinical study

In the *ex-vivo* pig liver model, significant differences in length and diameter of RFA-induced necrosis with variation of the electrosurgical parameters time, power and effect were observed. With an ablation time of 60-90 s using the bipolar soft coagulation mode, at 10 watts, effect 8 (equivalent to the recommendation of the manufacturer), a mean necrotic area of 22 mm × 9 mm (length × diameter) could be induced. Power seemed to have a more pronounced effect on tissue destruction when compared to time or mode. A power of 7 watts or less did not seem to produce a significant necrosis. Applying power in the range of 8-10 watts seemed to be most appropriate for intraductal biliary use and higher power was associated with deep tissue destruction (Figures 2 and 3).

Clinical study

In total, 19 RFA treatment cycles were performed in twelve patients (5 females, 7 males) with mean age of 70 years (median, 75; range, 33-85); Table 1, Figure 4.

All patients presented with malignant bile duct obstruction of the hepatic hilus (Klatskin like tumors). Final diagnosis included intrahepatic CCA in 2 patients, Bismuth stage IV in 8 patients, carcinoma of the gall bladder in two patients and metastases of gastric small cell carcinoma in one patient. Patients underwent either one (n = 9), two (n = 2) or five (n = 1) intraductal RFA applications that were considered technically successful during all applications. The ablations were applied to the left (n = 6), right (n = 9) or the main bile duct (n = 5) and RFA applications within one intervention ranged from 1 to 4 according to stricture length and/or bilateral *vs* uni-

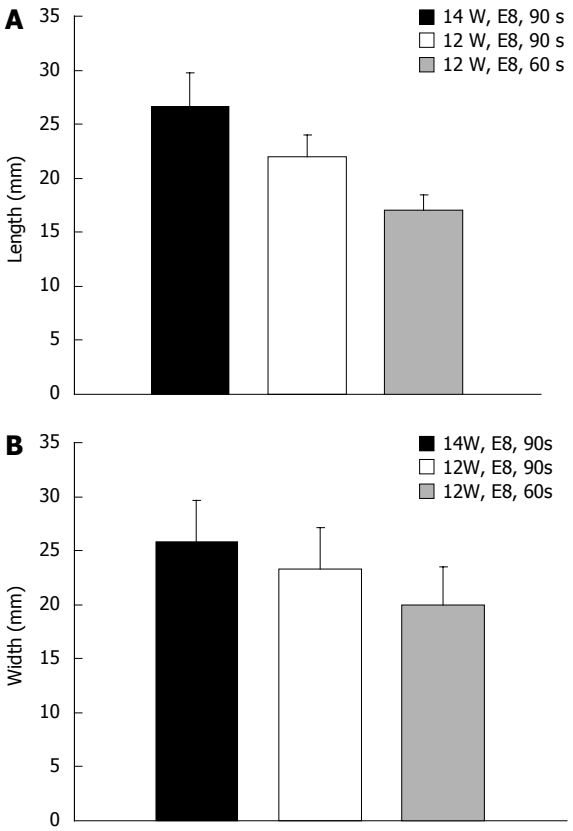

Figure 3 Results from the *ex-vivo* pig liver model. A: Length; B: Width. Varying electrosurgical variables revealed distinct differences in the extent of necrotic area. The used combinations are explained in the legend. *e.g.*, the blue column shows length and width of the necrosis caused by RFA with 14 watt, effect 8 with an ablation time of 90 s. RFA: Radiofrequency ablation.

Table 1 Overview of all patients treated with radiofrequency ablation for hilar malignancies included in our study

Patient	Patient gender/age	Tumor location	No. of RFA treatment cycles	Follow-up (mo)	Outcome
1	F/78	CCA Bismuth IV	2	6.4	Dead
2	F/73	Intrahepatic CCA	1	0.3	Dead
3	M/72	CCA Bismuth IV	5	19.8	Alive
4	M/85	CCA Bismuth IV	2	6.2	Dead
5	M/81	CCA Bismuth IV	1	1.1	Dead
6	M/33	Gastric carcinoma	1	Lost to follow up	-
7	F/77	Gallbladder cancer	1	6.6	Dead
8	F/78	CCA Bismuth IV	1	1.3	Dead
9	M/47	CCA Bismuth IV	1	14.1	Alive
10	F/78	CCA Bismuth IV	1	1.2	Dead
11	M/61	Gallbladder cancer	1	4.0	Alive
12	M/72	Intrahepatic CCA	1	2.9	Alive

The number of RFAs denotes the number of treatment cycles during follow-up. The number of follow-up months denotes the months from the first RFA in each patient. CCA: Cholangiocarcinoma; RFA: Radiofrequency ablation; F: Female; M: Male.

lateral tumor stenosis. Four of the patients who had been diagnosed with CCA were also treated with systemic chemotherapy (cisplatin plus gemcitabine).

We observed biliary bleeding 4 to 6 wk after the intervention in three patients and two of these patients died of hemorrhagic shock. While one of these patients developed spontaneous hemobilia, bleeding started during stent extraction in the other patients that was successfully stopped in one patient by insertion of a non-covered self-expanding metal stent (SEMS). None of the three patients had undergone chemotherapy concomitantly to endoscopic treatment. Of the remaining patients, four patients developed recurrent cholangitis during follow-up that could be successfully managed with stent exchange and antibiotic therapy.

From the time of the first RFA in each patient, the 30 and 90 d mortality of the entire cohort was 8.3% and 50%, respectively; Figure 5. The extrapolated median survival from the first RFA and the time of diagnosis were 6.4 (95%CI: 0.05-12.7) mo and 8.5 (95%CI: 4.6-12.4) mo, respectively.

DISCUSSION

Successful stenting of the biliary tree with prior or additive photodynamic therapy has been demonstrated to show the longest overall survival and has been referred to as the "gold standard" for endoscopic treatment of malignant biliary obstruction[5,13]. However, the management of patients treated with PDT is expensive and time consuming and more feasible endoscopic options with equal survival benefit are warranted. Endoscopically applicable RFA represents a novel expansion of a method that is well known from its percutaneous applications and which has shown promising results in recently published case series. However, the safety of endoscopic RFA for biliary malignancy has not yet been clearly defined. Clinical data on intrahepatic treatment of CCA are scarce and many of the published studies included mostly extrahepatic tumors (Table 2). We here report our own experience on performing endoscopic RFA in 12 patients with malignant bile duct obstruction (mostly Klatskin Bismuth IV) due to hilar tumors of different etiologies. In our study, the technical applicability of RFA procedures was found to be excellent, successful in all patients, and this is in line with previously published studies. Indeed, in the largest study published so far, the technical success rate was reported to be 95%[12].

Despite this, we did observe three cases of hemobilia that occurred 4-6 wk after RFA application. Two out of these three patients died from the consequences of hemorrhagic shock, while bleeding was successfully stopped in one patient by immediate SEMS insertion into the bleeding bile duct.

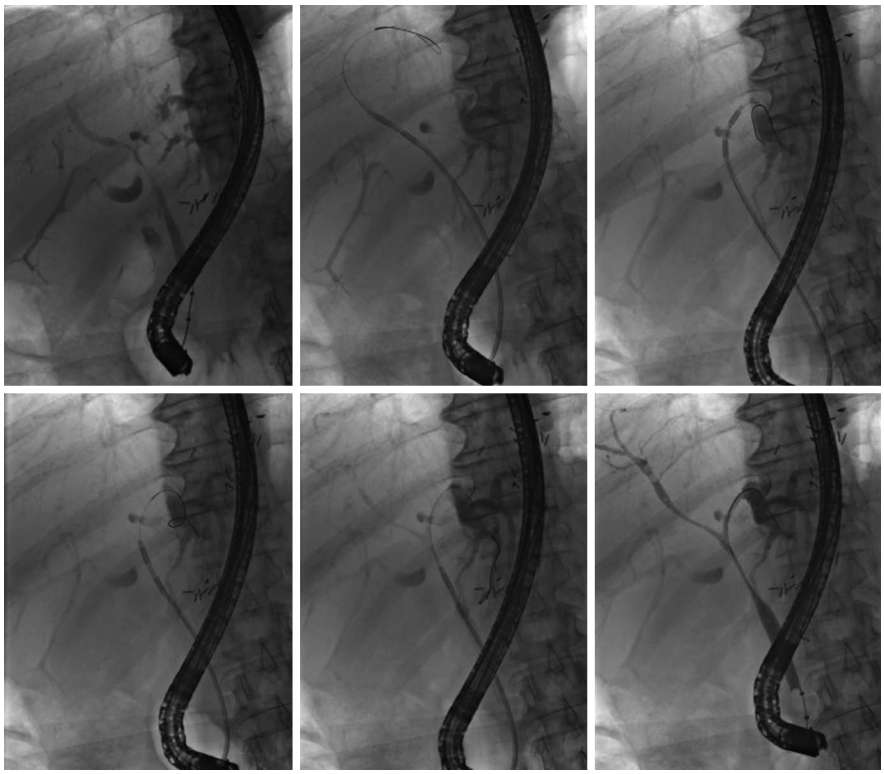

Figure 4 Application of endoscopically guided, intraductal radiofrequency ablation in a 72-year-old patient with an extended perihilar cholangiocarcinoma (Klatskin tumor, stage Bismuth IV, histologically proven) involving all subsegments. Multisegmental radiofrequency ablation (RFA) applications were performed (from left above to lower right). The patient experienced no treatment-associated complications and was doing well 15 mo after the initiation of endoscopic RFA treatment.

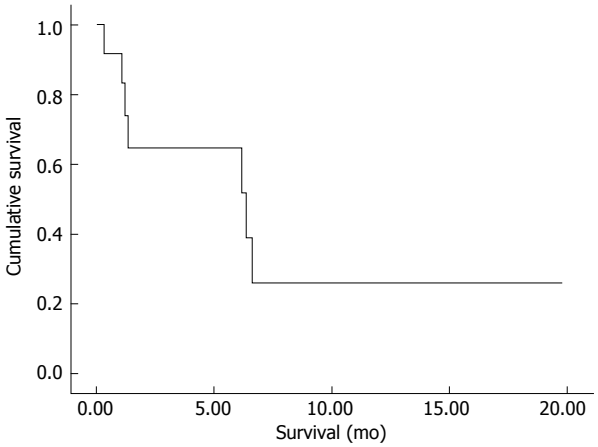

Figure 5 Kaplan-Meier survival curve of all study patients (*n* = 12). Calculation of survival started at the time of the first endoscopic radiofrequency ablation treatment in each patient.

Table 2 Literature overview of studies investigating the use of endoscopically-guided intraductal radiofrequency ablation in malignant biliary obstruction, localization of included tumors and complications are also listed for each study

Ref.	Year	*n*	Localization of the tumor	Complications
Figueroa-Barojas *et al*[15]	2011	8	Intra- and extra-hepatic	Pain: 4 Pancreatitis and Cholecystitis: 1
Steel *et al*[12]	2011	21	Extrahepatic	Empyema of the gallbladder: 1
Dolak *et al*[16]	2012	43	Intrahepatic	Hemobilia: 2 Liver infarction: 1 Empyema of the gallbladder: 1 Cholangitis: 1
Mizandari *et al*[17]	2012	39	Intra- and extrahepatic	Pain: 15
Own experience	2013	12	Intrahepatic	Hemobilia: 3 (2 deaths)

Although bleeding occurred several weeks after the RFA procedure in all three patients, a possible direct relationship to RFA may be assumed. In the two patients in whom bleeding occurred during stent extraction, deep necrosis induced by RFA may have been discarded from the perihilar tissue when necrotic material was removed while extracting the plastic endoprosthesis, thereby resulting in injury of a major blood vessel. Another possible explanation could be a strong necrotic effect induced by RFA that may have led to an increased angiogenic response within the tumor causing the recruitment of new vessel branches within the treated tissue. However, either of these hypotheses requires confirmation by analysis of immunohistochemical staining and biochemical processing of the treated tissues. Possible preemptive strategies to avoid biliary bleeding complications could include preinterventional investigation with intraductal ultrasound (IDUS) to rule out large blood vessels in the vicinity of the ablation site. For the prevention of late bleeding complications, insertion of a SEMS directly after the

RFA procedure seems to be feasible[12]. Severe complications associated with endoscopic RFA treatment have also been reported from most other published studies. For example, Dolak *et al*[14] reported that severe bleeding occurred in two of their patients and liver infarction in another patient, while Steel *et al*[12] reported that two of their patients required percutaneous gallbladder drainage for empyema.

Another secondary outcome measure of our study was overall survival following RFA therapy, which was shown to be 6.4 mo. In the above-mentioned Austrian multicenter study, the overall survival following RFA application was 10.6 mo. However, this was a multicenter cohort, involving 58 patients in total[14]. Other reported outcome measures included the increase of the diameter of tumor strictures[12] or stent patency at follow-up[12,14].

Taken together, our study shows that endoscopic RFA for malignant bile obstruction is a technically feasible and easy-to-apply procedure. However, based on the current experience, RFA should not be applied outside of study protocols given the risk of potentially fatal bleeding. Thus, randomized studies comparing PDT plus stenting *vs* RFA plus stenting, both with or without chemotherapy, are clearly desired.

COMMENTS

Background

Treatment with curative intent may be offered only for a minority of patients with cholangiocarcinoma. We evaluated the technical feasibility and safety of endoscopic radiofrequency ablation (RFA) for palliative treatment of malignant biliary obstruction.

Research frontiers

A new endoscopic RFA probe (Habib EndoHPB, EMcision United Kingdom, London, United Kingdom) has recently been CE and FDA-approved, thereby offering a new palliative treatment option for the therapy of malignant biliary strictures. The catheter can be positioned and applied during endoscopic retrograde cholangiopancreatography using a specific guidewire.

Innovations and breakthroughs

This study demonstrates that endoscopic RFA is easy to perform and a technically highly successful tool for the endoscopic treatment of biliary malignancies. However, severe bleeding occurred in three of our patients that may have been directly associated with RFA although it occurred several weeks after the respective RFA applications.

Applications

This study evaluates a new therapeutic approach in the palliative treatment of patients with malignant biliary obstruction.

Peer review

The authors showed in their retrospective study that endoscopic RFA is technically highly feasible for the treatment of malignant biliary strictures. However, severe complications such as biliary bleeding may occur and larger, prospective studies are warranted.

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BRIEF ARTICLE

A new peroral mother-baby endoscope system for biliary tract disorders

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Abstract

AIM: To investigate a new mother-baby system, consisting of a peroral cholangioscope and a duodenoscope in patients regarding its feasibility.

METHODS: In the study period from January 2007 to February 2010, 76 consecutive patients (33 men, 43 women; mean age 63 years old) were included in this pilot series. Endoluminal images and biopsies were obtained from 55 patients with indeterminate strictures, while 21 patients had fixed filling defects. The diagnostic accuracy of peroral cholangioscopy (POCS) in the visualization of strictures and tissue sampling was evaluated, and therapeutic success was monitored. Follow-up was performed over at least 9 mo.

RESULTS: A total of 55 patients had indeterminate strictures. Using the criteria "circular stenosis" and "irregular surface or margins", POCS correctly described 27 out of 28 malignant biliary strictures and 25 out of 27 benign lesions (sensitivity, 96.4%; specificity, 92.6%, diagnostic accuracy 94.5%). Visually targeted forceps biopsies were performed in 55 patients. Tissue sampling during POCS revealed malignancy in 18 of 28 cases (sensitivity: 64.3%). In 21 patients with fixed filling defects, 10 patients with bile duct stones were successfully treated with conventional stone removal. Nine patients with difficult stones (5 giant stones and 4 intrahepatic stones) were treated with visually guided laser lithotripsy. Two patients in the group with unclear fixed filling defects had bile duct adenoma or papillary tumors and were surgically treated.

CONCLUSION: The new 95 cm POCS allows for accurate discrimination of strictures and fixed filling defects in the biliary tree, provides improved sensitivity of endoscopically guided biopsies and permits therapeutic approaches for difficult intrahepatic stones.

Key words: Bile duct stenosis; Stones, Mother baby endoscopy; Peroral cholangioscopy; Cholangioscopy; Endoscopic retrograde cholangiopancreatography

Core tip: A new mother-baby system, consisting of a peroral baby cholangioscope and a maternal duodenoscope, was investigated in patients regarding its feasibility. Using the criteria "circular stenosis" and "irregular surface or margins", peroral cholangioscopy (POCS) correctly described 27 out of 28 malignant biliary strictures and 25 out of 27 benign lesions (sensitivity, 96.4%; specificity, 92.6%, diagnostic accuracy 94.5%). The new 95 cm POCS allows for accurate discrimination of strictures and fixed filling defects in the biliary tract, provides improved sensitivity of endoscopically guided biopsies and permits therapeutic approaches for difficult intrahepatic stones.

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INTRODUCTION

Strictures in the biliary system can lead to retention of bile, potentially resulting in jaundice, pain and fever, and are thus of great clinical importance. The differentiation between malignant and benign biliary strictures remains challenging, even with the use of transabdominal ultrasound (US), computed tomography (CT), and endoscopic retrograde cholangiography (ERC)[1]. Biliary strictures or filling defects can be caused by various inflammatory diseases, as well as by benign or malignant bile-duct tumors[2]. Malignant bile duct tumors, or so-called cholangiocarcinomas, are topographically categorized as intrahepatic or extrahepatic carcinomas[3]. Surgery is the only curative treatment for patients with cholangiocarcinoma, but the results have been more favorable for patients with early-stage disease. Therefore, a reliable diagnostic procedure is of great importance for these patients. Cholangiocarcinomas often grow longitudinally along the bile duct, rather than in a radial direction away from the bile duct. Consequently, imaging techniques, including ultrasound, CT, and magnetic resonance imaging are of limited sensitivity for the detection of cholangiocarcinoma. Therefore, biliary tissue collection during endoscopic procedures has been widely used to distinguish between benign and malignant strictures, thus providing the only definitive diagnosis that can be used to establish therapeutic strategies.

However, radiologically guided forceps biopsies, as well as brush cytology, has shown only limited sensitivity, usually approximately 40%-50%[4-6]. Furthermore, filling defects seen on ERC usually indicate the presence of bile duct stones, but these defects can also be caused by various benign or malignant tumors, including bile duct adenoma[7]. Intraductal tumors in the biliary tree can mimic large stones, and fixed filling defects that are thought to be intraductal polypoid lesions can also be stones.

Therefore, peroral cholangioscopy has been introduced to obtain visual images of the strictures, as well as visually guided biopsy[8]. Only direct endoscopic visualization of the bile duct enables a clear diagnosis of fixed filling defects and the undertaking of appropriate therapy. So far, conventional mother-baby endoscopes, such as the CHF-B20 or CHF-B30 long cholangio-pancreaticoscopes (usually longer than 160 cm), have been more demanding than the handling of short endoscopes, and thus, maneuverability inside the biliary system has been limited. In addition, the bioptic yield of the available very small biopsy forceps (outer diameter only 1 mm at the head) has been relatively poor. To overcome the aforementioned setbacks, a new, considerably shortened babyscope was developed, which allows for the insertion of a new, large-caliber biopsy forceps. The technical aspects have been presented in a separate manuscript.

The current study was designed to determine the feasibility of the new mother-baby system and to evaluate the diagnostic accuracy of a new peroral endoscope in patients with suspicious biliary strictures or fixed filling defects in the bile duct. The diagnostic accuracy of the new endoscope was consecutively evaluated in this pilot series over 2 years of continuous use in patients with unclear strictures and fixed filling defects, and patients were followed up over another 9 mo the verify their diagnoses.

MATERIALS AND METHODS

Patients

The study included 76 consecutive patients (33 men, 43 women, median age 63 years old) with obstructive jaundice, dilated ducts or fixed filling defects, who were treated by endoscopic sphincterotomy followed by intraluminal endoscopy from January 2007 until February 2010 in the Department of Gastroenterology at the Technical University Munich. The patients were followed up for at least 9 mo. The study was approved by the ethical committee (Ethical Committee TUM, decision from 08-14-2006). All of the patients included in this study agreed to be interviewed according to the study protocol. Written informed consent was obtained from all of the patients before ERC, cholangioscopy with a shortened peroral cholangioscope and endoscopically guided biopsy. All of the following inclusion criteria had to be confirmed: (1) clinical diagnosis of obstructive jaundice or other evidence of biliary stenosis; (2) unclear fixed filling defects or indeterminate strictures in the biliary tree suspected by transabdominal ultrasound; or (3) forceps biopsy during cholangioscopy in patients in whom strictures were observed, and stones could be excluded.

The exclusion criteria were as follows: (1) Previous surgery of the liver or bile duct, except for cholecystectomy (CHE); (2) a tumor in the main duodenal papilla; (3) histologically or cytologically confirmed carcinoma before cholangioscopy; or (4) previous photodynamic therapy for patients with cholangiocarcinoma. All 76 consecutive patients undergoing peroral cholangioscopy (POCS) to confirm a diagnosis of benign or malignant lesions and to evaluate the etiology of their lesions were included in this study. By the time of cholangioscopy, all of the patients had undergone ultrasound, but only 11 of 28 patients with malignant tumors had undergone additional CT scans and/or MRCP investigations before cholangioscopy. The reason for the divergent diagnostic procedures was that most of the patients were submitted for further clarification of an indeterminate stricture or fixed filling defect, and thus, the previous diagnostic procedure varied and could not be further investigated or compared.

Endoscopic equipment

The new mother-baby system was developed by one of

the authors (Frimberger E). ERC and endoscopic drainage were performed with a videoduodenoscope manufactured by Storz Company, in Tuttlingen, Germany. The technical details of the new mother-baby system are described in an accompanying publication in the same issue. The new babyscope was shortened by more than 1/3 the length of conventional long babyscopes. The instrumentation channel was enlarged, allowing for the insertion of large-caliber biopsy forceps with an outer diameter of the cups of 1.3 mm, which is an increase of 30% compared to conventional forceps. Corresponding to the shortness of the babyscope, the length of the forceps was shortened, thereby reducing the biopsy time considerably. The newly developed endoscopes and the large-caliber biopsy forceps were provided at no cost by Karl Storz GmbH and Co. KG, in Tuttlingen, Germany. Repairs were performed by the company without charge. There was no further financial support from any study sponsors.

Endoscopic intervention

During endoscopic retrograde cholangiopancreatography (ERCP), sedation with propofol and midazolam was administered. Endoscopic sphincterotomy (EST) was conducted using an Olympus papillotome (Olympus, Hamburg, Germany), introduced over a Terumo guide wire. The bile duct was selectively cannulated with the peroral short cholangioscope, without using a guide wire. During cholangioscopy, the mucosal appearance of the biliary stricture was evaluated on the basis of the cholangioscopic findings; histological results were not available at this time. The procedure was performed by two physicians: one handling the mother duodenoscope, and the other handling the short peroral cholangioscope. The passage into the subsegments of the biliary system often required steering by two examiners, and therapeutic procedures particularly required the control of two examiners. The laser device was the SMART Lithognost Laser from StarMedtec, in Starnberg, Germany. The fibers were 300 μm in diameter, and the average applied intensity was 100 J. The laser distinguished stones from the bile duct and could not be activated when in contact with the bile duct wall.

Criteria for endoscopic visualization of the bile duct (POCS): forceps biopsies

The findings of malignant strictures included the following: (1) circular polypoid tissue with visible stenosis and (2) a non-homogeneous surface or irregular margins. Benign strictures included the following: (1) smooth surface mucosa, without polypoid or papillary tissue and (2) regular margins. At least two cholangioscopic images or video documentations were recorded in detail in the medical charts by the POCS operator. Endoluminal forceps biopsy was performed under endoscopic guidance. The tip of the open forceps was approximately 3 mm wide. All of the ERC, POCS and biopsy procedures were performed by experienced endoscopists, who were aware of the results of the prior ultrasound examinations, the blood parameters of cholestasis, and the previous ERC results. Forceps biopsy was performed by conventional methods *via* the operating channel of the POCS. Exactly 2 biopsies were obtained. The first biopsy was acquired under perfect visual control. In some cases, when post-biopsy bleeding occurred after the first biopsy, visually controlled acquisition of the biopsy was hampered due to blurred vision. In these cases, the bile duct was flushed with fluid until clear visibility was obtained, and the second biopsy was performed under visual control of the area of interest.

Pathologists received the biopsies of indeterminate bile duct strictures without knowledge of the clinical background or the endoscopic images.

For the purpose of analysis, suspicions of carcinoma and carcinoma found in biopsy specimens were considered malignant. The final diagnosis was confirmed by surgical resection, histological results, or clinical follow-up over at least 9 mo. Benign biliary lesions were confirmed by surgery (n = 2), by negative histopathologic results, and by clinical follow-up over more than 9 mo, without clinical or radiologic evidence of malignancy.

RESULTS

Endoscopic peroral cholangioscopy: indications, complications, diagnosis and clinical follow-up

A total of 76 patients, 36 men and 40 women with a mean age of 63 years old (range 30 to 86 years), were enrolled. On the basis of ERCP findings, 55 patients were examined due to biliary strictures and 21 because of fixed filling defects in the biliary system. A side port duodenoscope was used in all of the cases. Two prototypes of the duodenoscopes were used in all of the patients without major repairs, and two cholangioscope prototypes were also used without major problems or major repairs. The short babyscope could be inserted into the biliary system in all of the cases. In particular, access to the side branches of the biliary system was easy because of the direct transmission of rotation exerted on the rear portion of the scope to its tip. Excellent transmission of shaft rotation was observed with the cholangioscope, enabling controlled passage into the intrahepatic side branches. The insertion of the 1.3 mm biopsy forceps was unproblematic and rapid, due to its considerably reduced length.

In all of the attempts, cannulation of the bile duct and POCS (n = 76) were performed successfully, without complications. The cholangioscope was easily introduced into the bile duct without the use of guide wires. Among the 55 biliary strictures, 28 were malignant, and 27 were benign. In the group with malignant cholangiocellular carcinoma (n = 24), 6 patients were surgically treated, 9 received or were enrolled for PDT treatment, and 9 patients received supportive care. Two patients in the group with benign strictures were confirmed by surgical resection (n = 2), and all of the other patients with benign strictures were monitored over at least 9 mo. The final diagnoses of the 55 patients with indeterminate strictures

Table 1 Final diagnoses of the 76 patients with indeterminate strictures (n = 55) or unclear filling defects (n = 21)

Type of stricture	No.	Final diagnosis		
		OP	Biopsy	FU
Indeterminate stricture		55		
Malignant stricture	28	5	15	8
Cholangiocarcinoma				
Gallbladder cancer				
Metastasis				
Benign stricture	27	2	-	25
Inflammatory changes				
Postoperative stricture after cholecystectomy				
Biliary filling defects	21	2	-	19
Gallstones				
Bile duct adenoma (low-grade dysplasia)				
Bile duct adenoma (high-grade dysplasia)				

FU: Follow-up.

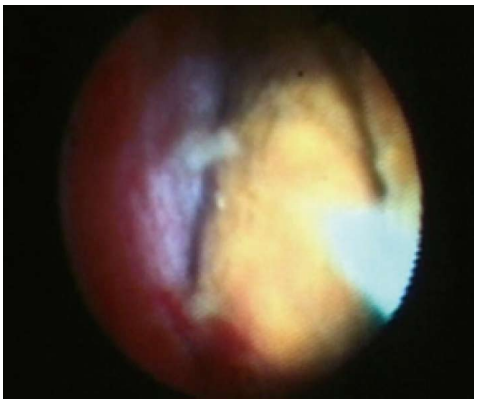

Figure 1 Peroral cholangioscopy aspect of a large bile duct stone. The stone was treated by visually guided laser lithotripsy and was completely removed. Overall, 4 giant stones and 5 intrahepatic stones with difficult access were completely removed.

and 21 patients with stones are listed in Table 1.

Endoscopic appearance of malignant and benign strictures: false negative and false positive endoscopic results during POCS and forceps biopsy

POCS alone identified 27 out of 28 malignant strictures (sensitivity, 96.4%). One patient with metastasis of an adenocarcinoma but an unknown primary tumor seemed to have benign pathology in the POCS investigation. All of the other patients fulfilled the criteria for having circular stenosis with irregular polypoid tissue. The diagnosis of malignancy was confirmed by histology, cytology, surgical resection or clinical course.

In the patients with benign strictures, there were 2 false-positive diagnoses among 27 benign strictures, according to the results of POCS observation. Twenty-five patients were correctly described as having benign strictures. Two patients with benign stricture had strictures that appeared malignant by POCS. These patients were operated on, but no cancer was identified. The biliary system was drained with a biliary anastomosis due to the long stricture. Overall, POCS alone identified 27 of 28 malignant strictures and 25 of 27 benign strictures from mucosal appearance, and the statistical values were thus calculated as follows: sensitivity: 96.4%; specificity: 92.6%; positive predictive value: 93.1%; and negative predictive value, 96.2%.

Endobiliary forceps biopsy during peroral cholangioscopy was performed in a total of 55 patients. Two subsequent biopsies were obtained in each patient, and biopsy acquisition was thus successful in all of the investigated patients. There were no complications related to tissue sampling. Tissue sampling correctly identified 18 of 28 malignant strictures in the bile duct and all 27 benign strictures (sensitivity, 64.3%; specificity, 100%; positive predictive value, 100%; negative predictive value, 73%).

Peroral cholangioscopy and fixed filling defects in bile duct

A total of 21 consecutive patients with suspected bile duct stones or unclear fixed filling defects were examined with the new cholangioscope. Detailed information regarding final diagnoses is provided in Table 1. In all 21 patients, initial ERCP with sphincterotomy was performed, and cholangioscopy was performed more than 4 d after the procedure. The cholangioscope was easily introduced into the biliary tract, including the right and left hepatic duct, in a time period shorter than 5 min. Typical features are shown in Figure 1, representing large intrahepatic stones. Nineteen patients had choledocholithiasis, and two patients had intrabiliary polyps. One patient with multiple fixed filling defects received a diagnosis of multiple bile duct adenoma with high-grade dysplasia, disseminated and continuously growing into the intrahepatic branches. One patient with a distal fixed filling defect was found to have adenoma of the bile duct, associated with a diagnosis of FAP.

Ten patients had bile duct stones, and all of the stones could be removed with a basket or balloon. In 9 patients, cholangioscopy revealed giant bile duct stones (n = 4) or intrahepatic bile duct stones not accessible by conventional methods (n = 5) (Figure 2). These stones were treated by visually guided laser lithotripsy and were subsequently successfully removed. Most of the stones were cleared in one session. Four patients had to undergo a second POCS to remove the remaining stones and to determine the absence of further stones.

In Figure 3A, the fluoroscopic ERC image of a patient with multiple fixed filling defects can be seen. The corresponding video of the POCS shows multiple bile duct polyps of papillary and polypoid shape, and the histological evaluation revealed adenoma with high-grade intraepithelial neoplasia. From the endoluminal aspects, a papillary neoplasm similar to intraductal mucinous neoplasia of the biliary system also appeared feasible. In this patient, liver transplantation was performed successfully. In Figure 3B, the ERC of a patient with intrahepatic gall stones in liver segment S7/8 is visualized, and the corresponding video showed detection of stones, which were treated by laser lithotripsy. In Figure 3C, a patient

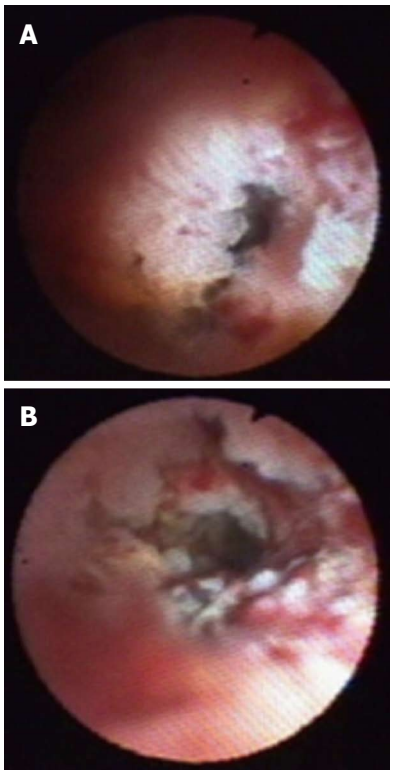

Figure 2 Cholangioscopic aspect of a malignant bile duct tumor. A circular stenosis can be seen, and irregular polypoid tissue with irregular margins indicates the cholangioscopic criteria for malignancy. A: Cholangoscopic aspect of a patient with hilar cholangiocarcinoma; B: Cholangioscopic picture of another patient with cholangiocarcinoma.

with hilar stenosis is presented. The corresponding video showed that when the scope was withdrawn from the right hepatic duct, no tumor could be seen. The left hepatic duct showed a high-grade stenosis. The stenosis of the left hepatic duct was passed, and withdrawal was performed from the left side. The patient was operated on with a hemihepatectomy and was cured of the tumor (R0 resection).

DISCUSSION

Peroral cholangioscopy has become an important additional tool for the investigation of biliary strictures and fixed filling defects. The practicability of the new mother-baby system was monitored in 76 patients with indeterminate strictures and filling defects, which are usually true challenges for diagnostic and therapeutic endoscopy. Intubation of the biliary system with the short babyscope was possible in all of the cases, without the use of a guide wire. The excellent direct transmission of shaft rotation to the tip of the babyscope, as a consequence of the shortened shaft (redesigned for optimal torque stability), facilitated intubation of the side branches of the biliary tree, thereby allowing passage into the deeper bile duct segments. The new large-caliber biopsy forceps could be easily inserted through the instrumentation channel of the babyscope, the diameter of which was larger than the channels of conventional babyscopes.

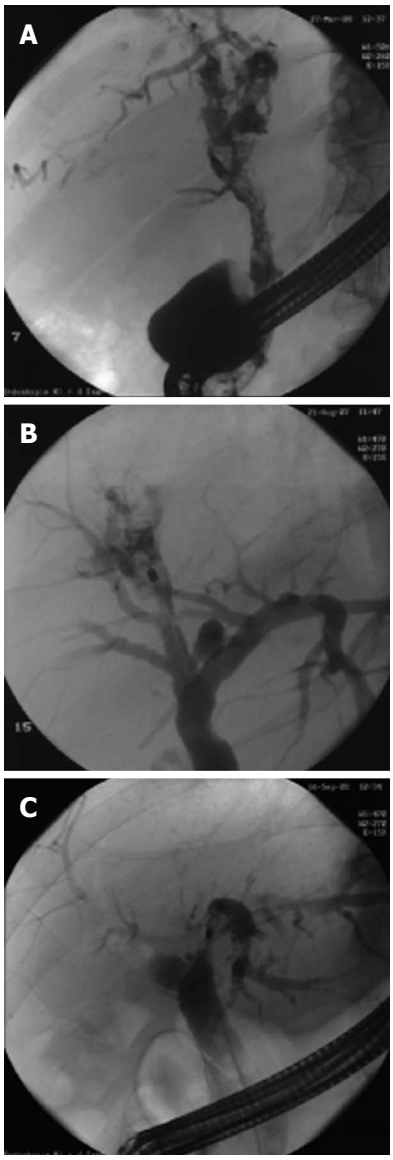

Figure 3 Endoscopic retrograde cholangiography fluoroscopic images and video illustrations of different cases. A: Patient with multiple papillary bile duct polyps; histology revealed adenoma with high-grade intraepithelial neoplasia, liver transplantation was successfully performed; B: Patient with intrahepatic stones (S7/8) treated by laser lithotripsy; C: Patient with stenosis of the left hepatic duct; histology revealed cholangiocellular carcinoma. Peroral cholangioscopy revealed that the right hepatic duct was without signs of infiltration, and left hemihepatectomy was successfully performed.

The new technical features of the shortened baby endoscope allowed for the determination of the true nature of undetermined bile duct strictures as diagnosed in an initial ERC, to obtain additional visual information about the shape and extent of a process and to obtain histological specimens with this process. Recent studies have suggested that the sensitivity of tissue sampling *via* fluoroscopically guided forceps biopsy was as low as 42%[4-6]. Thus, a more sensitive and accurate differentiation of malignant and benign bile-duct diseases is essential for the planning of appropriate therapy. Because the current study did not compare blinded forceps biopsy and brush cytology with POCS biopsy, a direct comparison between

radiologically *vs* endoscopically guided techniques could not be performed. Therefore, the sensitivity of forceps biopsy of 64% appeared to be in a similar range[4-6].

Various techniques for POCS have been used, and many types of babyscopes were developed between 1976[8] and the late 1980s[9-12]. More recent studies have confirmed that POCS is especially advantageous in the diagnosis of small mucosal biliary lesions when combined with narrow band imaging[13]. Modern POCS techniques have been further helpful in diagnosing early malignant changes in laterally spreading biliary tumor patients and in patients with persistent primary sclerosing cholangitis[14-16]. However, most of these POCS investigators used long endoscopes, with lengths greater than 160 cm, and some of the investigators complained about reduced maneuverability in small bile ducts and across strictures[11,12].

At present, the CHF-B20 and CHF-B30 systems are widely used for the diagnosis of lesions in the intrahepatic duct and the common bile duct[9-11,14-16]. Fukuda *et al*[17] used a variety of cholangioscopes in a large series undertaken over more than 12 years. This study reported high sensitivity in discriminating strictures from filling defects. In that study, 21 fixed filling defects of uncertain etiology were seen on ERC, but 8 of these uncertain filling defects turned out to be malignant diseases, including bile-duct cancers and cystic duct cancers. This observation is entirely in agreement with our recommendation that such unclear filling defects require further diagnostic approaches, and peroral cholangioscopy is especially suitable for this purpose. Fukuda *et al*[17] also reported that ERCP/tissue sampling correctly identified only 22 of 38 malignant strictures. These results are in close accordance with the data presented here, but the accuracy, sensitivity, and specificity of our technique appeared to be superior.

Recently, a new wire-guided cholangioscope, SpyGlass (Boston Scientific, Boston, MA, United States), was introduced as a new tool for cholangioscopy[18]. The SpyGlass system is a single-use, single-operator, intraductal system that allows for optical viewing and optically guided biopsies. In a recent study, Chen *et al*[18] reported that the rate of procedural success was 91%. Twenty patients underwent SpyGlass-directed biopsy, and the specimens procured from 19 patients (95%) were found to be adequate for histologic evaluation. The preliminary sensitivity and specificity of SpyGlass-directed biopsy to diagnose malignancy were 71% and 100%, respectively. SpyGlass-directed electrohydraulic lithotripsy succeeded in 5 of 5 patients (100%).

Also, overtube-balloon-assisted enteroscopy was recently used to place a guide wire for the positioning of an ultraslim endoscope (diameter < 6 mm) into the bile duct[19], which was considerably thicker than the babyscopes used here. The authors reported excellent feasibility and technical success in 12 of 14 patients. The use of ultraslim gastroscopes to perform choledochoscopy is, in fact, gaining popularity, and it was again reported using an overtube-balloon-assisted method for destroying large stones[20]. Because neither of the above systems was available in our center, comparative studies could not be performed.

Using the new technique with the Storz mother-baby system, we found the new shortened cholangioscope especially suitable for the evaluation and treatment of indeterminate strictures, as well as unclear filling defects. Indeterminate strictures were visually evaluated by well-defined morphological criteria: (1) circular polypoid tissue with visible stenosis; and (2) a non-homogeneous or erosive surface, with irregular margins. These criteria were chosen because bile duct cancers have previously been shown to be polypoid or papillary growing tumors associated with the formation of a stenosis[16,17]. Previous studies have found that cholangioscopy performed using two peroral cholangioscopes, the CHF-B20 (4.5 mm outer diameter) and the CHF-BP30 (3.4 mm outer diameter), typically revealed that the criteria for polypoid masses with stenosis, as well as irregular surfaces with erosions and/or ulcerations with irregular margins, were suitable for the description of 22 malignant tumors of the bile duct in 22 patients with PSC[16,17]. Using these 2 independent criteria, we found that 27 of 28 true-positive malignant tumors appeared malignant, and thus, the use of peroral cholangioscopy was highly sensitive. However, 2 of 27 patients with benign strictures also appeared malignant, and thus, over-diagnosis can result. However, it must be emphasized that such over-diagnosis can further occur with regard to the histological results obtained and interpreted after obtaining feedback. Most importantly, malignant tumors might thus not be overlooked. Also, laser lithotripsy was performed in our study through the new cholangioscope, including in 5 patients with difficult intrahepatic stones. All of the patients, especially those with intrahepatic stones, could be successfully treated, indicating that the new technique is a very useful tool, not only for diagnosis but also for the treatment of such diseases in particular.

In summary, the new peroral mother-baby endoscope system provided for easy diagnostic and therapeutic access into the common bile duct and the periphery of the biliary tract. The endoscopically chosen criteria for malignancy were adapted to previous findings and showed true-positive values in all of the cases, indicating that growth of polypoid tissue with irregular surfaces and margins is a true criterion for tumors. Vessel density on top could be additional information that is further investigated. Diagnostic and therapeutic accessories, such as large-caliber forceps or laser probes, were easily and quickly inserted through the short babyscope. Thus, the new system could become an essential tool for clinical centers focusing on biliary diseases.

ACKNOWLEDGMENTS

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COMMENTS

Background

Strictures in the biliary system can lead to retention of bile, potentially resulting in jaundice, pain and fever, and are thus of great clinical importance. The differentiation between malignant and benign biliary strictures remains challenging, even with the use of transabdominal ultrasound, computed tomography, and endoscopic retrograde cholangiography.

Research frontiers

Therefore, peroral cholangioscopy has been introduced to obtain visual images of strictures, as well as for visually guided biopsy. Only direct endoscopic visualization of the bile duct enables a clear diagnosis of fixed filling defects and the undertaking of appropriate therapy. So far, conventional mother-baby endoscopes, such as the CHF-B20 or CHF-B30 long cholangio-pancreaticoscopes (usually longer than 160 cm), are more demanding than the handling of short endoscopes, and thus, maneuverability inside the biliary system has been limited.

Innovations and breakthroughs

Peroral cholangioscopy has become an important additional tool for the investigation of biliary strictures and fixed filling defects. The practicability of the new mother-baby system was investigated in 76 patients with indeterminate strictures and filling defects, which are usually true challenges for diagnostic and therapeutic endoscopy.

Applications

Diagnostic and therapeutic accessories, such as large-caliber forceps or laser probes, were easily and quickly inserted through the short babyscope. Thus, the new system could become an essential tool for clinical centers focusing on biliary diseases.

Peer review

The new 95 cm peroral cholangioscopy allows for accurate discrimination of strictures and fixed filling defects in the biliary tract, provides improved sensitivity of endoscopically guided biopsies and permits therapeutic approaches for difficult intrahepatic stones.

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CASE REPORT

Confusing untypical intestinal Behcet's disease: Skip ulcers with severe lower gastrointestinal hemorrhage

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Abstract

Behcet's disease (BD) is a rare and life-long disorder characterized by inflammation of blood vessels throughout the body. BD was originally described in 1937 as a syndrome involving oral and genital ulceration in addition to ocular inflammation. Intestinal BD refers to colonic ulcerative lesions documented by objective measures in patients with BD. Many studies have shown that over 40% of BD patients have gastrointestinal complaints. Symptoms include abdominal pain, diarrhea, nausea, anorexia and abdominal distension. Although gastrointestinal symptoms are common, the demonstration of gastrointestinal ulcers is rare. This so-called intestinal BD accounts for approximately 1% of cases. There is no specific test for BD, and the diagnosis is based on clinical criteria. The manifestations of intestinal BD are similar to those of other colitis conditions such as Crohn's disease or intestinal tuberculosis, thus, it is challenging for gastroenterologists to accurately diagnose intestinal BD in patients with ileocolonic ulcers. However, giant ulcers distributed in the esophagus and ileocecal junction with gastrointestinal hemorrhage are rare in intestinal BD. Here, we present a case of untypical intestinal BD. The patient had recurrent aphthous ulceration of the oral mucosa, and esophageal and ileo-colonic ulceration, but no typical extra-intestinal symptoms. During examination, the patient had massive acute lower gastrointestinal bleeding. The patient underwent ileostomy after an emergency right hemicolectomy and partial ileectomy, and was subsequently diagnosed with incomplete-type intestinal BD by pathology. The literature on the evaluation and management of this condition is reviewed.

Key words: Intestinal Behcet's disease; Hemorrhage; Skip ulcers

Core tip: We present a patient with fever, abdominal pain and skip ulcers accompanied by lower gastrointestinal hemorrhage. Although the patient had undergone a number of examinations, no diagnosis was made. The patient underwent emergency surgery due to unmanageable lower gastrointestinal hemorrhage. Pathology of the resected bowel containing ulcer lesions indicated ectasia and blood vessel hyperplasia. The patient was diagnosed with incomplete-type intestinal Behcet's disease (BD). BD can influence any region of the gastrointestinal tract. It is more difficult to diagnose when intestinal BD is accompanied by multiple ulcers in various positions throughout the entire digestive tract.

Wang ZK, Shi H, Wang SD, Liu J, Zhu WM, Yang MF, Liu C, Lu H, Wang FY. Confusing untypical intestinal Behcet's disease: Skip ulcers with severe lower gastrointestinal hemorrhage. *World J Gastrointest Endosc* 2014; 6(1): 27-31 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i1/27.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i1.27

INTRODUCTION

Intestinal Behcet's disease (BD) refers to colonic ulcerative lesions documented by objective measures in patients with BD. Bechguard first described gastrointestinal involvement in 1940[1]. Oshima *et al*[2] reported that over 40% of BD patients had gastrointestinal complaints. Symptoms included abdominal pain, diarrhea, nausea, anorexia and abdominal distension[2]. Although gastrointestinal symptoms are common, the demonstration of gastrointestinal ulcers is rare. This so-called intestinal BD accounts for approximately 1% of cases[3,4].

The manifestations of intestinal BD are similar to other colitis conditions such as Crohn's disease or intestinal tuberculosis, therefore, it is challenging for gastroenterologists to accurately diagnose intestinal BD in patients with ileo-colonic ulcers. It is more difficult to diagnose when intestinal BD is accompanied by multiple ulcers in various positions throughout the entire digestive tract. Furthermore, giant skip ulcers and gastrointestinal hemorrhage are rare in intestinal BD. Here, we present a case of untypical intestinal BD. The patient had giant ulcers distributed in the esophagus and ileocecal junction accompanied by lower gastrointestinal hemorrhage, but no typical extra-intestinal symptoms.

CASE REPORT

A 47-year-old male presented to our hospital in October 2010 due to abdominal pain, fever and diarrhea. His abdominal pain was located in the epigastric region and lower right quadrant with no radiation. The pain was crampy and intermittent throughout the day. He could not recall what made the pain better or worse, but the symptoms had been present for approximately one year. In addition to fever and diarrhea the patient also experienced headache. His maximum temperature was 41 ℃. Endoscopy showed multiple giant ulcers in the esophagus and ileocolonic region. His clinical diagnosis was documented as Crohn's disease, and 5-aminosalicylate (mesalazine) 4.0 mg and prednisone 40 mg were administered orally. The above-mentioned symptoms gradually improved. However, his temperature rose when the dose of prednisone was tapered. The patient was referred to our hospital for further treatment.

The patient's past medical history consisted of recurrent oral aphthous ulcerations, folliculitis and facial acne-like lesions from 2009. He also had a history of chronic headaches. He denied ever using alcohol, tobacco products or illicit drugs. His family history was only significant for peptic ulcer disease and diabetes mellitus. On physical examination, his body temperature was 39.5 ℃, heart rate was 102 bpm and arterial blood pressure was 126/72 mmHg. There was some aphthous ulceration on the oral mucous membrane and multiple acne-like lesions on both cheeks and the neck. His abdominal pain was located in the epigastric region and lower right quadrant without rebound tenderness. On examination of the crissum, no ulceration was observed. The results of clinical laboratory tests and examinations are shown in Table 1. Based on these results it was hoped to discriminate intestinal BD from Crohn's disease. The patient was treated with oral prednisone 40 mg/d and a proton pump inhibitor. During further examination, the patient had massive acute lower gastrointestinal bleeding. Bleeding was located in the ileocecal region by emergent colonoscopy. A few oval ulcers were found around the crissum (Figure 1C). We were unable to achieve hemostasis by medical treatment. A surgical consult was obtained, and the patient underwent an emergency right hemicolectomy and partial ileectomy with ileostomy. During surgery, we observed that the wall of the cecum was thick and the lumen between the ileum and colon was filled with blood. Macroscopic examination of the resected material showed occasional discoloration in the serosa, mucosal edema, an ulcer (4 cm × 4 cm) and occasional necrosis in a segment 32 cm in length involving the ileocecal region (Figure 1D). On microscopic examination of the ulcer involving the serosa, there was mixed-type purulent cell infiltration rich in neutrophils, congestion and capillary proliferation. There was considerable thickening of some arterioles and venules, lymphocyte infiltration in and around the vessel wall, thrombus and recanalization in some vessels at the base of the ulcer (Figure 2). Treatment with oral prednisone 40 mg/d and thalidomide 300 mg/d was started after dermal sutures were removed. The abdominal symp-

Table 1 Results of clinical laboratory tests and examinations

Clinical examinations	Results
Routine blood examination	White blood cells 14400/μL, red blood cells 408 × 10^4/μL, hemoglobin 11.6 g/dL, hematocrit 35.7%, platelets 220 × 10^4/μL, C-reactive protein 38.9 mg/dL, blood sedimentation 58 mm/h
Routine stool examination	White blood cells, 20-30/HP; red blood cells, filled visual fields
Blood biochemistry	Total protein, 8.6 g/dL; AST, 36 IU/L; ALT, 32 IU/L; LDH, 171 IU/L; and total bilirubin, 0.2 mg/dL
Bacteriologic culture of blood, urine, and stool	Negative
Serum antinuclear antibody and antituberculosis antibody	Negative
PPD skin test and T-spot test	Negative
Pathergy test	Positive
Gastroscopy	Giant ulceration in the inferior extremity of the esophagus (Figure 1A)
Colonoscopy	A large ulcer in the ileo-cecal junction (Figure 1B)
Pathological examination of the endoscopic biopsy specimen	Nonspecific ulceration
Abdominal CT imaging	Thickening of the intestinal canal of the ascending colon and ileocecal region
Whole gastrointestinal barium meal examination	Inflammatory changes in the ascending colon and ileocecal region

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; CT: Computed tomography.

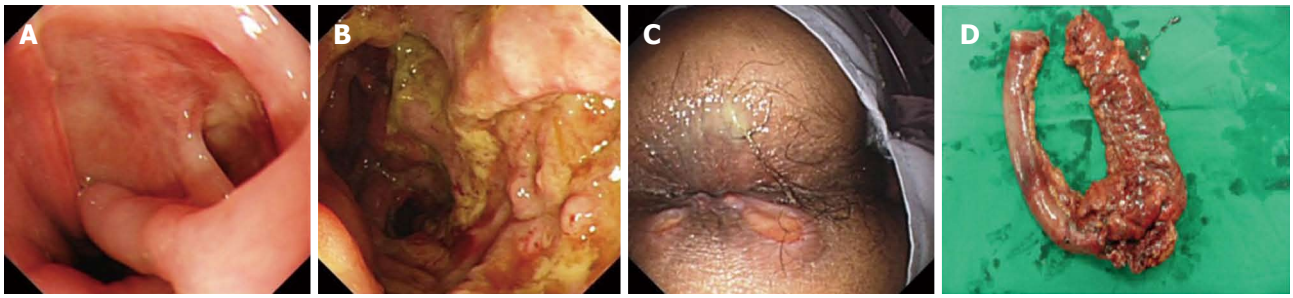

Figure 1 Positive manifestations in examination and in the surgically resected segment. A: A giant and ovoid ulceration in the inferior extremity of the esophagus; B: A typical oval-shaped large ulcer at the ileocecal junction; C: A few oval ulcers around the crissum; D: The resected material showed that the wall of the cecum was thick, occasional discoloration in the serosa, mucosal edema, an ulcer (4 cm × 4 cm) and occasional necrosis in a segment 32 cm in length involving the ileocecal region.

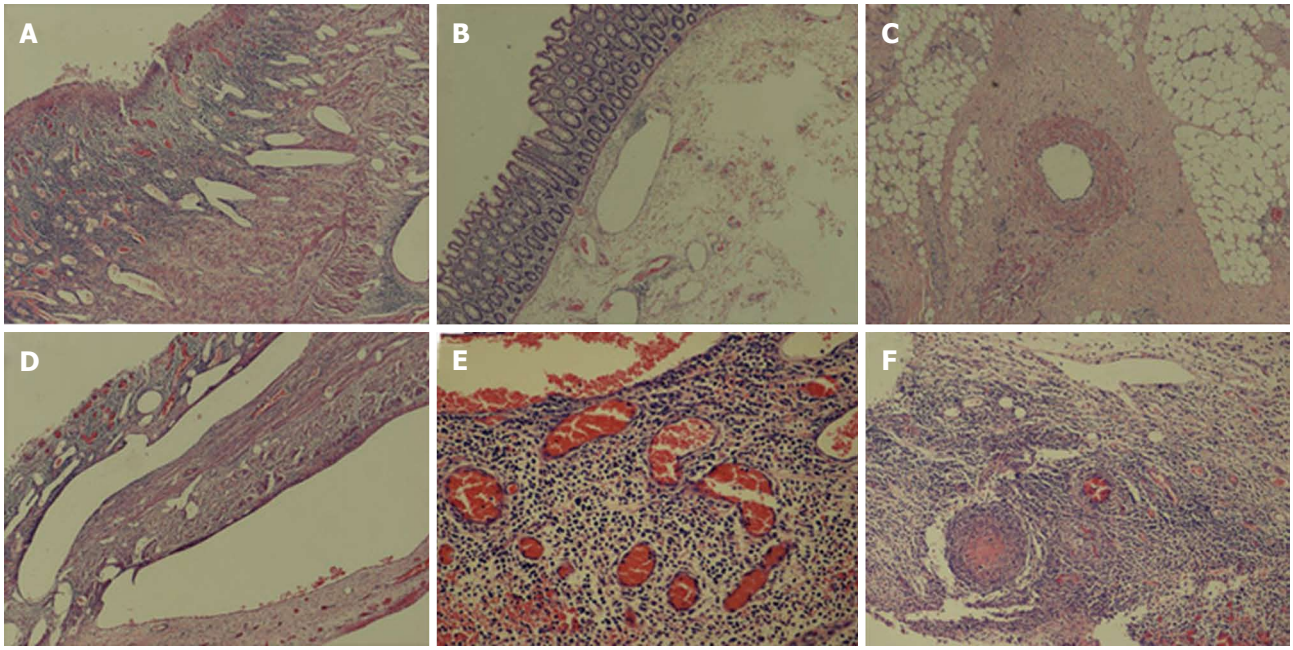

Figure 2 Positive pathological manifestations in the surgically resected segment. A: The ulcer in the ileocecal lesion encroached the whole segment with ectasia and blood vessel hyperplasia [hematoxylin and eosin (HE), × 40]; B: Ectasis in blood vessels was observed in normal tissues around the lesion (HE, × 40); C: The thickened vessel intima with lymphocyte and polymorphonuclear leukocyte infiltration (HE, × 40); D: Extreme ectasia in lesion blood vessels (HE, × 40); E: There was considerable lymphocyte infiltration in and around the vessel wall (HE, × 200); F: Thrombus and recanalization in some vessels at the base of the ulcer (HE, × 100).

toms and crissum ulcers gradually improved, and he was discharged 2 mo after admission.

DISCUSSION

BD is a rare and life-long disorder characterized by inflammation of blood vessels throughout the body[5]. BD was originally described in 1937 as a syndrome involving oral and genital ulceration in addition to ocular inflammation[6]. Since then, BD has been recognized and many other manifestations have been added to the original triad. The etiology of BD is unknown. To date, research has revealed that infectious, autoimmune and genetic mechanisms may cause this disease[7]. BD mostly affects children and young adults between the second and fourth decades of life[8]. Those affected before the age of 25 years (early onset) and males have been shown to have more severe disease symptoms[9].

Intestinal BD occurs most frequently along the ancient Silk Road which extends from the Far East to the Mediterranean basin. The prevalence varies widely among geographic locations. In Japan, the prevalence rate is 10 in 100000, in Saudi Arabia it is 20 in 100000, and in Northern Europe and in the United States it is only 0.3 per 100000. The male-to-female ratio also varies by geographic location. Men predominate in Egypt, Turkey, Israel, and Iran, whereas women predominate in Europe, the United States, and Japan. The age of onset can range from infancy to the 70s, although the highest frequency occurs in the third and fourth decades. Involvement of the gastrointestinal tract is variable in different populations, being more common in Japan (50%-60%) and less common in the Mediterranean basin, including Turkey (0%-5%)[1]. Although the reasons for this peculiar geographic distribution of intestinal BD are unknown, it may provide clues for the elucidation of putative etiological

Table 2 Diagnostic Criteria (Behcet's Disease Resarch Committee of Japan, 1987)

Maior
Recurrent aphthous ulceration of the oral mucous membrane
Skin lesion
Erythema nodosum
Subcutaneous thrombophlebitis
Folliculitis, acne-like lesion
Cutaneous hyperirritability
Eye lesion
Iridocyclitis
Chorioretinitis, retinouveitis
Definite history of chorioretinitis of retinouveitis
Genital ulcer
Minor
Arthritis without deformity and ankylosis
Gastrointestinal lesion characterized by ileocecal ulcers
Epididymitis
Vascular lesion
Central nervous system symptoms
Diagnosis
Complete type:4 major features
Incomplete type:
3 major features
Major + 2 minor features
Typical ocular symptom + 1 major or 2 minor features
Suspected type:
2 major features
1 major + 2 minor

Table 3 Guideline Statements for Diagnosis of Intestinal Behcet's Disease (Japan)

Diagnosis of intestinal Behcet's disease can be made if
There is a typical oval-shaped large ulcer in the terminal ileum or
There are ulcerations or inflammation in the small or large intestine;
And clinical findings meet the diagnostic criteria of Behcet's disease

agents or genetic factors that might be associated with intestinal BD.

BD can influence any region of the gastrointestinal tract. The mouth is the most common gastrointestinal site affected by BD followed by the ileocecal region[10]. Intestinal lesions are located on the antimesenteric side. Gastrointestinal symptoms related to BD include abdominal pain, nausea and vomiting. Some rare symptoms are present in emergency conditions, such as intestinal perforation or bleeding[11,12].

There is no specific test for BD, and the diagnosis is based on clinical criteria. In Japan, diagnostic criteria for BD have been established by the BD Research Committee (Tables 2, 3)[13,14]. Based on these criteria, the present case was a suspected type of BD. The patient was subsequently confirmed to have incomplete-type intestinal BD by pathology. It can be difficult to diagnose untypical intestinal BD. Moreover, intestinal BD manifests mainly in the terminal ileum, and esophageal lesions are rare. The patient had esophageal and terminal ileum ulcers accompanied by recurrent oral aphthous ulcerations, similar to Crohn's disease. Inflammatory bowel diseases should be kept in mind in the differential diagnosis of intestinal BD. Although International Study Group criteria for BD accurately distinguish between BD and Crohn's disease[15], there are some common features. Similar to Crohn's disease, BD manifests as discrete intestinal ulcers and discontinuous bowel involvement. Both of these diseases share extra-intestinal manifestations, such as arthritis and uveitis. Rectal sparing is common in both diseases. Intestinal lesions in Crohn's disease tend to be longitudinal ulcers with a cobblestone appearance, while those in BD are round and oval "punched-out" ulcers. Moreover, epithelioid granuloma is one of the pathological characteristics of Crohn's disease, whereas it is uncommon in intestinal BD. Another feature of Behcet's colitis is lymphocyte venulitis, which is a type of vasculitis. Despite these differences, it can be difficult to differentiate between these two diseases.

Ten percent of patients with BD accompanied by intestinal involvement require surgical treatment. The complications most frequently requiring surgery are perforation and bleeding. The recurrence rate after surgery has been reported to be 40%-87.5% and frequently appears at the anastomosis site. If suitable medical treatment is given after surgery, this condition can be improved. Thalidomide is a synthetic glutamic acid derivative first introduced in 1956 in Germany as an over-the-counter medication. The Food and Drug Administration approved its use in the treatment of erythema nodosum leprosum. Furthermore, it was shown to be effective in unresponsive dermatological conditions such as actinic prurigo, adult Langerhans cell histiocytosis, aphthous stomatitis, Behçet's syndrome and others. Zhang *et al*[16] reported a 29-year-old patient with a five-year history of BD who was administered prednisone and thalidomide. The patient was well with blood sedimentation and C-reactive protein in the normal range. Sayarlioglu *et al*[17] reported a patient with intestinal BD and recurrent perforating intestinal ulcers under immunosuppressive treatment with methylprednisolone and cyclophosphamide. The patient's symptoms did not disappear until she was treated with thalidomide[17]. These reports suggest the beneficial effects of thalidomide in BD. Direskeneli *et al*[18] revealed that thalidomide decreased TNF-alpha receptor levels, $CD8/CD11b^+$ T cells and natural killer cells during early treatment and increased $CD4^+CD45RO^+$ memory T and $gammadelta^+$ T cells during longer treatment in patients with BD. Therefore, thalidomide, in small doses, was thought to be safe and effective in the treatment of intestinal BD, was not addictive and did not have acute side-effects such as motor impairment.

In conclusion, practitioners should be aware of intestinal BD which accompanies intestinal ulcers and could lead to perforation or hemorrhage. Urgent surgical resection is mandatory in the case of hemorrhea without effective medical treatment, and medical treatment is required after surgery.

COMMENTS

Case characteristics

The patient had fever and abdominal pain, accompanied with skip ulcers with

lower gastrointestinal severe hemorrhage.

Clinical diagnosis

The case should be diagnosed as untypical Intestinal behcet's disease (BD).

Differential diagnosis

The case should be difference from Crohn's disease and gastrointestinal tuberculosis.

Laboratory diagnosis

Serum antinuclear antibody, antituberculosis antibody, PPD cutantest and T-spot test were all negative, but pathergy test was positive.

Imaging diagnosis

Endoscopy displayed giant ulceration in the inferior extremity of esophagus and the ileocecal junction, abdominal computed tomography imaging indicated the intestinal canal of ascending colon and ileocecal region was thicken, and whole gastrointestinal barium meal examination presented the inflammatory change of ascending colon and ileocecal region.

Pathological diagnosis

Pathological examination of the endoscopic biopsy specimen indicated nonspecific ulcer, but the ulcer of ileocecal lesion resected by surgical encroached whole range with ectasia and hyperplasia blood vessels.

Treatment

The patient underwent an emergency right hemicolectomy and partial ileectomy with ileostomy because of unmanageable lower gastrointestinal severe hemorrhage, and continued the treatment of prednisone and thalidomide.

Related reports

BD can influence any level of the gastrointestinal tract. The mouth is the most common gastrointestinal sites affected by BD. Next site is the ileocecal region. Intestinal lesions are located on the antimesenteric side. Gastrointestinal symptoms related to BD are abdominal pain, nausea and vomiting. Some rare symptoms present in emergency conditions, such as intestinal perforation or bleeding. The manifestations of intestinal BD similar to other colitis such as Crohn's disease or intestinal tuberculosis, therefore it is still challenging for gastroenterologist to accurately diagnose intestinal BD among the patients with ileo-colonic ulcers. Meanwhile it was more difficult to diagnose when intestinal BD accompanied with multiple ulcers in different positions of whole digestive tract. Furthermore skip giant ulcers and gastrointestinal hemorrhage are rare in intestinal BD.

Experiences and lessons

Clinical practitioners should be aware of intestinal BD which accompanies intestinal ulcers since the case probably could lead to perforation or hemorrhage. Urgent surgical resection is mandatory in case of hemorrhea without efficient medical treatment. And the medicinal treatments are still needed after surgery.

Peer review

The authors have presented a rare disorder of BD. The case reported here is interesting.

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REVIEW

Modern approach to cholecysto-choledocholithiasis

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Abstract

Gallstones and common bile duct calculi are found to be associated in 8%-20% of patients, leading to possible life-threatening complications, such as acute biliary pancreatitis, jaundice and cholangitis. The gold standard of care for gallbladder calculi and isolated common bile duct stones is represented by laparoscopic cholecystectomy and endoscopic retrograde cholangiopancreatography, respectively, while a debate still exists regarding how to treat the two diseases at the same time. Many therapeutic options are also available when the two conditions are associated, including many different types of treatment, which local professionals often administer. The need to limit maximum discomfort and risks for the patients, combined with the economic pressure of reducing costs and utilizing resources, favors single-step procedures. However, a multitude of data fail to strongly demonstrate the superiority of any technique (including a two or multi-step approach), while rigorous clinical trials that include so many different types of treatment are still lacking, and it is most likely unrealistic to conduct them in the future. Therefore, the choice of the best management is often led by the local presence of professional expertise and resources, rather than by a real superiority of one strategy over another.

Key words: Laparoscopy; Endoscopy; Laparo-endoscopic; Endoscopic retrograde cholangiography; Bile duct stones; Cholecystolithiasis; Common bile duct stones; Laparoendoscopic rendezvous

Core tip: There is no consensus on the correct strategy for the care of simultaneous gallbladder and common bile duct stones. Many therapeutic options are available, including laparoscopic, endoscopic, percutaneous and open traditional techniques, either through a combination of these treatments or by conducting them in a stepwise sequence.

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INTRODUCTION

Common bile duct stones (CBDS) occur in 8%-20%[1,2] of patients suffering from gallstones, although actual incidences of CBDS in this patient group could be higher. The association of these two conditions can lead to many severe complications, such as acute biliary pancreatitis, jaundice and cholangitis, transforming the choice of the best strategy for treating a benign issue into a potentially life-threatening problem. Although some authors have advocated for a "wait and see" policy for asymptomatic gallbladder stones[3], almost none could propose the same approach if CBDS are detected as well[2,4]. Nonetheless, a

significant paper also reported a conservative (no action) behavior for silent CBDS found during routine intraoperative cholangiogram (IOC)[5]. Moreover, in the case of patients with severe comorbidity unfit for surgery and symptoms of CBD obstruction (jaundice, cholangitis, recurrent acute pancreatitis), the sole execution of a formal endoscopic retrograde cholangiography (ERCP) is often obligatory, leaving the gallbladder *in situ*[6]. However, a Cochrane review failed to confirm the imperative necessity of an immediate ERCP to relieve acute pancreatitis without sepsis[7]. A very intriguing observational study from Sweden[8] reported a so-called "paradigm shift" from open choledochotomy and cholecystectomy toward bile duct clearance using the endoscopic route and selective laparoscopic cholecystectomy in patients suffering from cholecysto-choledocholithiasis (CCL).

While the "gold standard" of treatment for gallstones has been laparoscopic cholecystectomy (LC) since the early 1990s[9,10] and ERCP is considered optimal for isolated CBDS[4], no consensus exists to address CCL[11,12]. The European Association for Endoscopic Surgery published the comprehensive guidelines of minimally invasive approaches in 2006, but no robust statements were published regarding the best treatment for CCL[13].

Many therapeutic options are available, including laparoscopic, endoscopic, percutaneous and open traditional techniques, either as a combination in a concurrent manner or as a stepwise sequence.

The choice of the best strategy is often led by the local presence of professional expertise and resources, rather than by a real superiority of one strategy over another[12,14-18].

However, the current standard of treatment for CCL is influenced by many different professionals, including gastroenterologists, anesthesiologists, surgeons and endoscopists, leading to some conflict regarding organizing approaches for treatment.

We performed a PubMed, Embase and Cochrane bibliographic search for CCL, updated in October 2013, by manually searching for interesting cross-matched references. Reporting on more recent articles, randomized clinical trials (RCTs) and meta-analyses was considered a priority. Intrahepatic bile duct stones represent a less common disease with several peculiar pathological etiologies and will not be considered further in this review. Despite some differences in the epidemiologic features of gallstones and CCL, a special effort was made to include papers published from all over the world, including North America, Europe and Asia.

DIAGNOSIS OF COMMON BILE DUCT STONES

The first crucial issue for correctly managing CCL is to reach a good diagnosis in order to reduce unplanned procedures, unnecessary invasive exams and under treatment. Traditionally, the gold standard of diagnosis is achieved by cholangiography, which can be conducted by means of an intraoperative route (injecting the contrast medium through the cystic or the common bile duct), by an endoscopic papillary injection or even by a percutaneous approach. All methods are, of course, invasive.

Since the advent of laparoscopy, the preoperative diagnosis of CBDS has become increasingly popular due to the need for avoiding laparoscopic IOC and further treatments that were, at the beginning of the experience, highly demanding. Moreover, the widespread adoption of ERCP, even as a diagnostic tool, enormously impacted the development of some excessively invasive algorithms due to success rates of CBD clearance of almost 98% in the hands of experienced endoscopists[19].

Currently, IOC is routinely performed in some centers[20-22] and selectively in others[23,24], while it is easily reproducible by the majority of surgeons. Nevertheless, the definitive acceptance of one policy over another has not been confirmed[25], with selective IOC having some advantages in terms of a shorter operating time and fewer perioperative complications but at the price ofa higher readmission rate if CBDS are subsequently detected[22]. Moreover, laparoscopic CBD exploration is becoming more popular, while intraoperative or postoperative ERCP is also safe and effective. However, current good practice should reserve the use of ERCP for those patients with CBDS as a therapeutic strategy only in selected doubtful cases[18] due to the possibility of complications[26-28] and false-positives.

Many of the diagnostic flow-charts and algorithms proposed consider a baseline stratification of the risk of having CBDS, including ultrasonography dilatation of the CBD and biochemical parameters, such as gamma-glutamyl transpeptidase, transaminases, alkaline phosphatase, bilirubin and lactatedehydrogenase. All of these markers are combined in predictive models[16,29] to reserve more invasive or expensive imaging - cholangiography by ERCP or IOC, magnetic resonance cholangiography (MRC) and endoscopic ultrasonography (EUS) - for higher-risk patients, although no clinical-laboratory parameter is able to predict CBDS with optimal accuracy[30].

Currently, the most important preoperative diagnostic tools are MRC and the traditional ultrasound[31-35]. Alternatively, the policy of routine MRC was not found to be cost-effective in patients without symptoms or suspicion of CBDS, whereas IOC during LC was the best strategy[36]. Interestingly, some authors reported[37] the routine use of IOC during LC, even after MRC and successful preoperative ERCP, to detect residual CBDS. Indeed, due to the higher sensibility of IOC over MRC, it could be hypothesized that there is no need to conduct preoperative MRC in those patients suspected to have CBDS who are already scheduled for an intervention[38].

Recently, introducing EUS added a new tool to the diagnostic algorithm of CDS. Despite the relatively scarce use of this technique among many hospitals worldwide, its routine use, at least in patients with intermediate and high risk of CBDS[39-42], could play an important role for the next future two-stage strategy. A proposed rational

sequence could reserve EUS for those patients with intermediate to high risk of CBDS and a negative MRC[43]. A realistic and intriguing new proposal could consider the adoption of EUS in selected patients suspected to have CBDS, followed by a consecutive session of ERCP[44].

The role of the CT scan in detecting CBDS is quite marginal, and its use is limited by the low frequency of radiopaque stones and cut-off size[45]. However, it may be useful when a silent incidental stone is found.

CCL

There are many options to treat CCL, but each one has different advantages and limitations. Few trials have demonstrated robust evidence of one method's superiority over another. The local availability of both technical resources and professional expertise could also play a pivotal role in deciding which treatment to administer.

Open surgery

From a historical point of view, CBD exploration has been performed at the same time as a cholecystectomy by open choledochotomy with papillotomy and stone extraction, often with a T-tube placement, with an unacceptable morbidity and mortality[11,46]. Therefore, it was proposed to abandon this method on a routine basis 20 years ago[47]. A more recent retrospective series reported good results with primary closure of choledochotomy where endoscopic and minimally invasive facilities are not available[48]. Currently, open choledochotomy and papillotomy could still play a role in those cases with intraoperative unexpected diagnosis of choledocholithiasis and cholangitis, with bile duct dilatation or where all other endoscopic, percutaneous and laparoscopic approaches failed. Open choledochotomy and papillotomy could also be used in the case of a pre-existing open surgery that limits the application of endoscopic approaches (*i.e.*, Roux-en-Y intestinal reconstruction after gastrectomy)[11].

Preoperative ERCP (and sub-sequential laparoscopic cholecystectomy)

A CBD clearance can be carried out by ERCP with endoscopic sphincterotomy (ES) before LC in many cases, and it is most likely the most common strategy used in the majority of hospitals worldwide[4]. As previously reported, due to its intrinsic invasiveness, ERCP should be proposed for those patients with confirmed bile duct stones only. Furthermore, there is the possibility of some increased difficulty when performing LC after an endoscopic procedure[49]. Thus, this two-stage strategy raises the problem of a close sequence of pre-endoscopic imaging through conventional US, MRC or EUS and a following LC within a maximum of 72 h that, practically, leads to some organizational problems in a busy hospital setting. The other drawback of any two-stage procedure is that the patient undergoes two different uncomfortable anesthesiologic sessions.

Postoperative ERCP (after laparoscopic cholecystectomy)

In those patients with a lower risk of CBDS, a policy of selective IOC and ERCP after LC seems to be rational[50]. Similar situations are represented by intraoperative diagnosis of CBDS when an endoscopist or a surgeon trained to perform a laparoscopic bile duct clearance is not available in the operating theatre or in those cases of misdiagnosed CBDS discovered only after LC. Obviously, two anesthesiologic sessions are needed, which are likely to disturb the patient. Lastly, the main risk of such an approach is to fail a complete bile duct clearance postoperatively and to then have to conduct further procedures[51].

Intraoperative ERCP (with concomitant laparoscopic cholecystectomy)

The single-stage laparoendoscopic treatment, known as the "Rendez-vous Technique" (RVT), is used to indicate simultaneous LC and intraoperative ERCP, facilitated by papilla visualization and cannulation through a guide-wire the surgeon inserts into the cystic duct. The technique was first described almost 20 years ago[52-54], and hypothetically, it combines many advantages, such as minimal invasiveness and an acceptable learning curve, at the price of some organization troubles between endoscopists, surgeons and operating room personnel[55-57], but is yet to be accepted. A robust review by La Greca *et al*[58] analyzed data from 27 papers, which included almost 800 patients and compared the RVT to other approaches. This research showed an overall bile duct clearance of 92.3% and few complications (1.6%-6% bleeding from the sphincterotomy and 1.7%-7% pancreatitis). These advantages are related to the use of a guide wire that allows a facilitated cannulation of the papilla without the risk of irritating the pancreatic duct.

The initial drawback of the endoscopic step completed in the supine position of the patient has not been confirmed[59]. Many experiences were reported in the literature[60-63], confirming safety, excellent CBD clearance percentages, and short learning curves. The adjunct of the intraoperative procedure does not prolong hospitalization of routine LC[64].

Concomitant laparoscopic cholecystectomy and common bile duct exploration

One possible exciting and rational option to address CCL is conducting laparoscopic CBD exploration (LCBDE) during routine LC[65]. In this case, the surgeon is able to resolve the patient's disease completely during the same session, avoiding the risks of sphincterotomy[26] and without the need to conduct further treatments. Additionally, the abovementioned preoperative step of diagnosis could be outdated (an IOC is mandatory before LCBDE). Some surgeons with sufficient expertise in advanced laparoscopy have proposed LCBD as an excellent option for CCL[66,67], but acceptance of such a technique in most hospitals is far off due to its steep learning curve, especially when a T-tube has to be used[68].

Table 1 Comparison of the available approaches to concomitant lithiasis of gallbladder and common bile duct

	Advantages	Disadvantages	Risks	Availability
Single-step				
Open cholecystectomy and bile duct clearance	Highly effective	Highly invasive	Surgical complications, Kehr positioning	All hospitals
Fully laparoscopic cholecystectomy and bile duct clearance	Very effective	Highly less invasive	Kehr positioning	Few hospitals
Laparoscopic cholecystectomy and intraoperative endoscopic bile duct clearance	Very effective	Less invasive	Endoscopic complications	Few hospitals
Two-step				
Preoperative endoscopic bile duct clearance and sequential laparoscopic cholecystectomy	Very effective	Less invasive	Unnecessary ERCP, Endoscopic complications	Most hospitals
Laparoscopic cholecystectomy and sequential endoscopic bile duct clearance	Effective	Less invasive	Endoscopic complications, Further procedures	Most hospitals

ERCP: Endoscopic retrograde cholangiography.

Moreover, the surgeon's experience influences the choice of technical procedure, such as the extraction of stones by the transcystic route[69] rather than performing a choledochotomy or the decision to do primary closure versus T-tube placement[70].

None of these differences, however, impacted the patients' final outcomes. One of the most challenging maneuvers during LCBDE is the placement of a T-tube after closing the choledochotomy, but the real advantages, in terms of postoperative morbidity, of such a procedure are not confirmed according to a recent review article and meta-analysis[71].

Shifts between the approaches and other techniques

The spectrum of variability of the different approaches is prone to some percentage of failure. Notwithstanding these limitations, almost each of these techniques can be used if one does not work, raising the overall success rates. For example, the RVT could be attempted in the case of uncompleted preoperative ERCP caused by a difficult papillary approach[72]. Alternatively, if the guidewire insertion through the cystic duct during the RVT is not possible, a skilled endoscopist is able to complete the one-stage procedure through a conventional intraoperative ERCP[57]. Moreover, a failed preoperative or intraoperative ERCP could lead to an LCBDE or an open intervention, while a second-look at a multiple-session ERCP (often with stenting) is always possible with the help of shock-wave technologies or percutaneous trans-hepatic treatments[73-75].

COMPARING THE DIFFERENT TECHNIQUES

In times of reduced resources, it is of utmost importance whether the one-stage management of patients with CCL is associated with reduced costs compared with a two-stage procedure[76]. However, the economic pressure should be balanced with some learning curve to gain experience with more recent mini-invasive single-stage strategies, with the goal of similar patient outcomes. A summary of the pros and cons of each different strategy is shown in Table 1.

One of the first logical consequences of introducing ERCP in almost all hospitals was limited mass open operations, while advanced laparoscopy led to comparing the open procedure and CBD clearance with the total laparoscopic approach. LCBDE was confirmed to be superior compared to open surgery in terms of mortality and morbidity (but less effective for common bile duct clearance) since 2006[77]. Theoretically, LCBDE minimizes the risks of post-ERCP complications[26-29] and the need for further anesthesia, with an excellent success rate of stone extraction (more than 90%)[67,77]. However, LCBDE remains limited to centers with advanced laparoscopic expertise[12].

Furthermore, the high availability of ERCP in almost all hospitals limited the mass of such study designs, and the acceptance of the superiority of LC over open operation avoided further protocols. Indeed, one recent prospective trial comparing LCBDE and open surgery confirmed the superiority of the laparoscopic method in terms of efficiency, morbidity and mortality[78].

When comparing the two-stage (LC with preoperative or postoperative ERCP) and single-stage (LC with LCBDE), no significant differences were found, except for some intrinsic characteristics (fewer therapeutic sessions)[79,80]. Another trial[81] reported having a reduced hospital stay when using LCBDE.

A very recent review and meta-analysis[82] of six RCTs comparing prospectively preoperative ERCP and RVT concluded that the latter method resulted in a reduced incidence of endoscopy-related pancreatitis and a shorter hospital stay, although stone clearance and overall morbidity were almost equivalent. Another meta-analysis[83] included RVT in the so-called one-stage procedure, merging studies regarding LCBDE and comparing this group to the two-stage procedures (LC preceded or followed by ERCP). Again, no statistically detectable differences in patients' outcomes were recorded between the two strategies.

Another review[84], conducted only by comparing two-stage procedure clearance versus RVT, found a reduced incidence of postoperative pancreatitis with the latter method (2.4% instead of 8.4; OR, 0.33; 95%CI: 0.12-0.91, $P = 0.03$). Another group[85] published the results of a

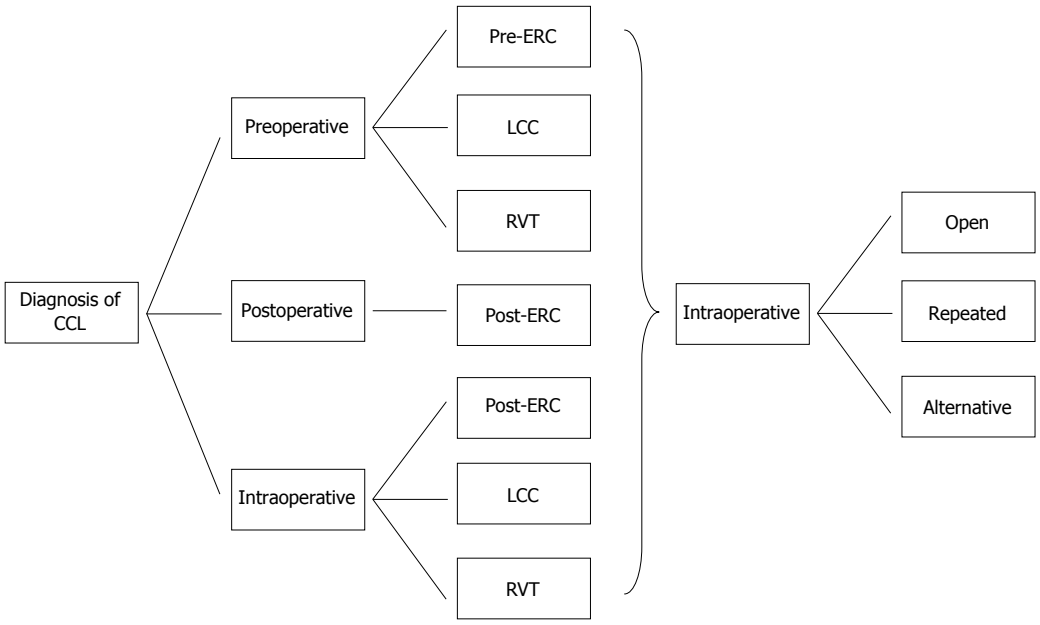

Figure 1 A proposed algorithm for a combined-multimodal approach to cholecysto-choledocholithiasis. CCL: Cholecysto-choledocholithiasis; ERC: Erythropoietin-responsive cells; RVT: Rendez-vous Technique; LCC: Laparoscopic cholecystectomy.

comparative study of 200 patients, suggesting the superiority of RVT over preoperative ERCP in terms of hospital stay. In contrast, the RCT published by Rábago *et al*[86] reported similar percentages of CBD clearance between the two approaches. A study by Hong *et al*[87] compared LCDE and RVT, and no differences were found between the two groups regarding duration of surgery, success rate, complications, retained stones, hospital stay, and costs. Another study[88] also reported similar ductal stone clearance rates, although LCBDE was associated with shorter hospital costs.

The most updated and comprehensive review of available literature likely was published in 2013 by the Cochrane Group[89]. After a careful and rigorous selection, only 16 RCTs, including a total of 1758 patients, were taken into consideration. The trials compared most of the options available to treat CCL. Although the authors advised about the high risk of bias, they found no significant difference in the mortality and morbidity between open surgery versus ERCP clearance (1% *vs* 3%, 20% *vs* 19%, respectively). However, patients who received open surgery had fewer retained stones (6% *vs* 16%).

Again, there was no significant difference in the main outcomes between LCBDE and pre-operative ERCP. Similar results were found when comparing trials on LCBDE *vs* RVT or post-operative ERCP. Interestingly, there was a detectable difference in the numbers of retained stones between LCBDE and postoperative ERCP (9% *vs* 25%). Therefore, single-staged LCBDE *vs* two-staged pre-operative or post-operative ERCP appeared to lead to comparable results in terms of mortality and morbidity, with a non-significant difference in the percentage of retained stones in the single-stage group (8% *vs* 14%, $P = 0.94$). The authors concluded that open bile duct surgery seems superior to ERCP in achieving CBDS clearance, but data referred to the early endoscopy era.

Presently, no single study comparing the whole spectrum of treatments (preoperative, postoperative ERCP, LCBDE, RVT) has been published, most likely due to the unrealistic contemporaneous presence of so many professionals and dedicated resources in the same facility. In our department, for example, there is a great availability of very skilled endoscopists (three professionals) who are able to manage intraoperative ERCP with challenging situations, while MRC needs a long time to be scheduled due to a very busy imaging service. However, it is very difficult to schedule several LC within an appropriate time after a preoperative ERCP, which is to be balanced with oncologic patients. Therefore, our approach to CCL is usually based on the RVT[57].

From a theoretic point of view, the best approach should be that in which all options are available in the same facility, modulating each one according to the single patient. Moreover, in the case of failure, other options could be proposed to guarantee a successful CCL resolution. A proposed algorithm is shown in Figure 1.

CONCLUSION

The current management of CBD stones associated with gallstones requires an adequate approach due to the possibility of perioperative morbidity and mortality with severe impact on the quality of life. Many strategies are available at present, mostly involving LC as a pivotal step in the entire process. The extremities of the spectrum of treatments are represented by open traditional surgery and full laparoscopic cholecystectomy with CBD clearance. However, in the majority of hospitals worldwide, ERCP is the preferred choice used to complete an LC. Timing of the ERCP (preoperative, intraoperative or

postoperative) is often dictated by the local presence of professional expertise and resources, rather than by a real superiority of one method over another. However, data refer to the early spectrum of treatments, which are influenced by economic pressure to prefer single-stage management approaches.

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MINIREVIEWS

Transnasal endoscopy: Technical considerations, advantages and limitations

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Abstract

Transnasal endoscopy (TNE) is an upper endoscopy method which is performed by the nasal route using a thin endoscope less than 6 mm in diameter. The primary goal of this method is to improve patient tolerance and convenience of the procedure. TNE can be performed without sedation and thus eliminates the risks associated with general anesthesia. In this way, TNE decreases the cost and total duration of endoscopic procedures, while maintaining the image quality of standard caliber endoscopes, providing good results for diagnostic purposes. However, the small working channel of the ultra-thin endoscope used for TNE makes it difficult to use for therapeutic procedures except in certain conditions which require a thinner endoscope. Biopsy is possible with special forceps less than 2 mm in diameter. Recently, TNE has been used for screening endoscopy in Far East Asia, including Japan. In most controlled studies, TNE was found to have better patient tolerance when compared to unsedated endoscopy. Nasal pain is the most significant symptom associated with endoscopic procedures but can be reduced with nasal pretreatment. Despite the potential advantage of TNE, it is not common in Western countries, usually due to a lack of training in the technique and a lack of awareness of its potential advantages. This paper briefly reviews the technical considerations as well as the potential advantages and limitations of TNE with ultra-thin scopes.

Key words: Transnasal endoscopy; Transoral endoscopy; Ultra-thin endoscopy; Sedated endoscopy; Unsedated endoscopy

Core tip: Transnasal endoscopy with ultra-thin endoscopes improves patient tolerance and convenience of the procedure, prevents the risks associated with general anesthesia, and decreases the cost and total duration. However, there are some drawbacks of the procedure with the technical limitations of scopes. These are discussed briefly in this review.

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INTRODUCTION

Conventional transoral endoscopy (TOE) is the standard diagnostic method used to visualize the upper part of the gastrointestinal tract, including the duodenum. It can be performed without sedation, using only a topical oropharyngeal anesthesia such as lidocaine spray, or under sedation, which generally results in better patient tolerance and comfort. Sedated TOE is more common in most developed countries, including Western Europe and

the United States[1,2]. However, sedated TOE increases the risk of adverse cardio-respiratory events, especially in elderly patients and patients with co-morbidities, and requires careful patient monitoring and increased nursing time, which can increase the cost of the procedure[3-6]. Therefore, routine diagnostic TOE is currently being done without sedatives, using only topical or pharyngeal anesthesia, in many high volume endoscopy centers[7,8]. This approach significantly increases patient discomfort, which decreases the tolerability of the procedure, and thus could potentially decrease the quality of examination as a result of retching and general patient discomfort[9,10].

Unsedated transnasal upper endoscopy (TNE) using ultra-thin endoscopes (UTE), where the outer diameter is less than 6 mm, has been introduced as an alternative method to both sedated and unsedated TOE[11-15]. TNE has been performed predominantly in primary care health institutions and in private clinics to facilitate comfortable endoscopy without requiring sedative drugs[16-18]. Several studies have reported that unsedated TNE is safe, well tolerated and significantly reduces patient discomfort when compared to unsedated TOE[18-20]. TNE is also comparable to sedated TOE in terms of patient tolerance and comfort but is safer and cheaper than sedated TOE since it does not require deep anesthesia[21-24].

As mentioned above, although the advantages of TNE have been shown in a wide range of studies from many countries, there is a significant geographic disparity in the usage of unsedated TNE[19,25]. In Far East Asia, particularly Japan, TNE is very popular among endoscopists and nearly half of all endoscopies are currently done by the transnasal route[19,26]. However, in Western countries, approximately 2/3 of endoscopists are not aware of the advantages associated with this method or do not have the required training to perform TNE. A survey among 624 endoscopists from different European countries revealed that only 31% of respondents practice the procedure and 34% of them lack any formal training in the transnasal approach[27]. In addition, 74% of endoscopists practicing TNE use this technique in less than 20% of all eligible patients. In this survey, the most common responses for not adopting TNE into daily practice were uncertainties about its potential advantages and lack of training in the procedure. The reasons for its limited use by endoscopists trained in the procedure were concerns about image quality and maneuverability. This survey elucidates that many endoscopists are still not familiar with TNE and that there is great need to discuss the technical aspects and potential advantages of this novel endoscopic method.

TECHNICAL CONSIDERATIONS OF TRANSNASAL ENDOSCOPY

Transnasal endoscopes, also known as small-caliber, ultra-thin or ultra-slim endoscopes, are very similar to standard or slim endoscopes except for their outer diameter, which is less than 6 mm, and their working channel, which is usually only 2 mm in diameter. There are small differences in the outer diameter of transnasal scopes among different manufacturers. Scopes with outer diameters from 5 to 6 mm usually have both up-down and right-left knobs, similar to standard endoscopes. Transnasal scopes in which the outer diameter is less than 5 mm generally only have an up-down knob. The working length, bending capability and field of view for transnasal endoscopes are usually comparable with standard endoscopes. However, their working channel is not suitable for standard biopsy forceps and other endoscopic catheters. Thus, they require special biopsy forceps to enter through the narrow working channel. Their aspiration capacity is also limited due to the narrow working channel when compared to standard endoscopes with a working channel of at least 2.8 mm. A color image can be generated in transnasal endoscopes by a charge-coupled device (CCD) camera located in the tip of the scope. The image quality of transnasal endoscopes is comparable to that of standard endoscopes and previous studies were unable to find significant differences in their diagnostic capabilities when compared to standard endoscopes[22,28]. They do not require special video processors and light sources and are compatible with model processors of their manufacturer. They do not have high-definition video capture capabilities but some models have advanced imaging features such as narrow-band imaging[29]. The numbers of procedures that can be performed with an ultra-thin endoscope, as well as the cost of scopes and the length of warranty, are comparable to standard endoscopes. Reimbursement rate of TNE is same with unsedated TOE in most countries or they are paid under the same codes.

The main concern during a nasal endoscopic procedure, for both the endoscopist and the patient, is passing the scope through the nasal passageway. This makes nasal pretreatment and the application of local anesthesia one of the most critical aspects of the procedure. The methods for nasal pretreatment in TNE are not standardized[30]. The most common practice starts by applying topical lidocaine to the nostrils. A vasoconstrictor such as naphzoline or oxymetazoline may also be applied to facilitate decongestion. Topical anesthesia of the oropharynx with 1-2 sprays of lidocaine is also recommended. This allows the endoscopist to switch to an oral endoscope easily should the transnasal route fail. Using a special nasal catheter coated with an anesthetic gel can achieve good local anesthesia throughout the nasal passageway (see Figure 1). It is applied through the nostril which allows the patient to breathe the most easily and is removed after 4 to 5 min. The diameter of a 14/16 F catheter is very similar to the diameter of ultra-thin endoscopes, making it ideal for anesthetic gel application. Many studies addressing the utility of TNE have only used topical lidocaine application to the nostril using a spray or gauze/cotton swab instead of catheters for pretreatment, which makes good local anesthesia deep inside the nasal passage unlikely[18,21,31-33]. We believe pretreatment using a 14/16 F catheter to apply an anesthetic gel is the most

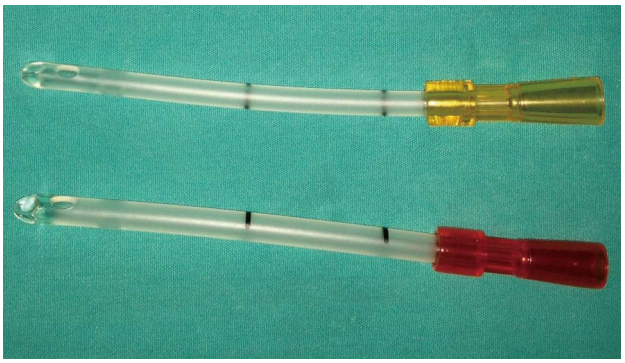

Figure 1 Pretreatment delivery catheter for transnasal endoscopy (Fujinon, Fujilm, Japan).

reliable method to increase the tolerability and comfort of TNE. In our daily practice, we use a combination of lidocaine spray and a lidocaine coated catheter for an effective anesthesia.

TNE is usually done when the patient is in the left lateral position. In special circumstances, it can also be performed in the sitting position. The understanding and orientation to the nasal anatomy facilitates transnasal endoscope insertion. Lubrication of the endoscope tip will help the passage into the nasopharyngeal space. The endoscope can be passed either along the floor of the nose or between the middle and inferior turbinate. It is important to apply gentle pressure on the shaft of the scope and avoid sudden movement as it enters the nose in order to prevent intranasal pressure and patient discomfort. Nasopharyngeal closure, tongue base, hypopharynx, vocal fold motion and pooling of oral secretions should all be evaluated during the procedure. The patient's head should be flexed forward as the scope is passed into the upper esophageal sphincter. The patient should be asked to swallow as the scope is gently advanced, air is insufflated into the esophagus, and the entire length is then evaluated. At this point, the upper GI examination can be completed in an identical manner to a standard oral endoscopic procedure. If a biopsy sample is needed, it can be obtained using dedicated 1.8 mm biopsy forceps for TNE. During the removal of the endoscope, the tip should be kept in the middle of the lumen by hand control to prevent rubbing to the nasal septum and turbinates.

ADVANTAGES OF THE TRANSNASAL ROUTE

The greatest advantage of TNE when compared to conventional unsedated TOE is that it provides a more comfortable and tolerable procedure for the patient. The nasal route is less sensitive than the uvula, palatine arches and base of tongue, which minimizes the gag reflex and increases patient tolerance. Most studies comparing TNE with conventional unsedated TOE found that TNE is better tolerated and considerably reduces nausea, gagging, choking and overall patient discomfort[5,10,11,20,22,26]. In a current prospective, randomized study, our group compared TNE, using a 5.9 mm diameter ultra-thin endoscope, with unsedated TOE, using a 9.3 mm standard endoscope, in 400 patients undergoing an upper endoscopy for dyspeptic symptoms[34]. All patients were asked to complete a questionnaire using a 10 cm (10 point) visual analog scale (VAS) after the procedure. Mean VAS scores for throat pain, retching, breathlessness, abdominal discomfort/pain, tolerability, overall distress and difficulty of the procedure were significantly lower in TNE patients when compared to TOE patients (Table 1). A repeat procedure, if needed, was significantly more acceptable for TNE patients when compared to TOE patients (82.4% and 60.5%, respectively).

Table 1 Patients' evaluation of transnasal endoscopy and transoral endoscopy by visual analog scale (mean ± SD)[34]

Evaluation criteria	TOE	TNE
Pain inside the nose[a]	1.2 ± 0.7	3.4 ± 1.9
Pain in the throat[a]	4.3 ± 2.5	1.7 ± 0.8
Retching and breathlessness feeling[a]	5.4 ± 3.1	2.1 ± 1.4
Abdominal discomfort and pain[a]	3.9 ± 1.7	2.3 ± 1.2
Tolerability[a]	4.8 ± 2.4	2.6 ± 2.1
Overall distress and difficulty[a]	4.4 ± 2.9	3.1 ± 1.8

TNE: Transnasal endoscopy; TOE: Transoral endoscopy. Visual analog scale: 0 = none; 10 = unbearable. [a]$P < 0.05$.

The results of studies comparing TNE with sedated TOE are controversial in terms of patient tolerance and acceptability. Stroppa *et al*[21] reported that TNE without sedation was better accepted than conventional sedated TOE in 30 patients who underwent both procedures on consecutive days. However, patient tolerance has been found to be similar or better in sedated TOE when compared to unsedated TNE in other studies[35-37]. Sedation, in general, causes extension of the total procedure time and increases the overall cost of the procedure[22,38]. In comparison to sedated TOE, TNE had fewer adverse effects on cardiopulmonary function and the autonomic nervous system[22,37,39]. This is likely due to the fact that TNE, with an ultra-thin scope, induces less sympathetic stimulation and causes smaller changes in both blood pressure and heart rate. In most studies, TNE was found to be safer, did not result in any adverse cardiovascular effects and showed a smaller reduction in oxygen saturation when compared to conventional TOE[22,37]. Most morbidity and mortality associated with upper endoscopic procedures are related to sedation[4,6]. Therefore, unsedated TNE prevents many side effects associated with endoscopy and eliminates the risks of upper endoscopy attributed to sedation. In addition, no intravenous line is necessary on a routine basis. TNE is also likely to be safer in elderly and bedridden patients with a high risk of aspiration pneumonia[3] since TOE may stimulate salivary secretion and increase the risk of aspiration.

TNE decreases the total expense of the endoscopic procedure by eliminating the need for sedation, seda-

Figure 2 Relative diameters of an ultra-thin endoscope (left, 5.9 mm) and a standard gastroscope (right, 8.8 mm).

tion-related complications, sedation-related work loss, post-procedural monitoring and post-procedure transportation. In several studies, the cost-effectiveness of unsedated TNE was investigated. They found that the mean procedure time, recovery time and cost of unsedated TNE was significantly lower than sedated TOE[12,40].

Lastly, during unsedated TNE the patient is able to speak and observe the procedure. This provides a significant advantage over sedated TOE since patients can discuss the endoscopic images with the endoscopist during the procedure and the endoscopist can see the nasal cavity, pharynx, larynx and vocal cords. Since TNE does not require a mouthpiece, it is also a useful technique in patients with dental problems or unconscious patients who cannot open their mouth. TNE can also be performed in the sitting position which may be an advantage in patients who have difficulty lying down. The nasal endoscope is very thin in appearance when compared to standard endoscopes and this may contribute to patient satisfaction visually (Figure 2).

LIMITATIONS OF THE TRANSNASAL ROUTE

The most important concern in nasal endoscopy, for both the endoscopist and patient, is passing the scope through the nasal passageway. From the patient's perspective, the most unfavorable side effect of TNE is nasal pain and nasal discomfort. Some patients may think that the insertion through nose is more irritating hypothetically, even before the procedure. Younger patients are generally more sensitive than elderly patients and have more discomfort during the insertion and withdrawal of the scope[41]. If patients have a recent history of rhinitis or other nasal problems, this may increase nasal sensitivity and result in greater pain and discomfort. In our study, patients in the TNE group reported significantly more nasal pain than those in the TOE group (Table 1) but most of them marked it as tolerable. In another study, in which TNE patients were specifically asked about pain, 55% of patients reported that the most painful region was the nose during the procedure. However, 65% of the patients who underwent a TOE in the same study also reported that the pharynx was the most painful region[42]. In another study, discomfort during the insertion was reported at the same rate in TNE and sedated TOE groups[21]. Pain during insertion was reported at the same rate among TNE, unsedated conventional TOE and ultra-thin TOE groups in a randomized trial[43]. These results show that some patients may suffer from nasal pain and discomfort during nasal insertion of the endoscope but it is generally well tolerated and comparable to pain and discomfort caused by oral insertion. Nasal pretreatment and application of an appropriate local anesthesia are likely the most critical procedures to reduce nasal pain and increase patient tolerance. The experience of the endoscopist will also affect the severity of nasal pain and discomfort of the patient. To our knowledge, there is currently no published data on this but we have observed that patients usually reported greater pain when the endoscopist was in the learning phase of TNE, especially in first cases.

The most significant and common complication of TNE is epistaxis[19,26]. It is reported as between 1% to 5% in clinical studies and generally described as mild, self-limited, stopping within a few minutes of the termination of the procedure, and not requiring any intervention[18,21,22,25,42-44]. No epistaxis was reported with scopes under 5 mm in diameter[45,46]. The rate of epistaxis was 4% in our studies using a 5.9 mm scope, which was comparable to what is published in the literature[47]. We observed that epistaxis was often related to a recent history of rhinitis which had not been reported previously by the patient. We suggest that in patients with a recent history of rhinitis, TNE should be postponed or TOE should be preferred. The difficulty in withdrawing the scope has not been reported in the literature but a presentation reported that it is a rare complication (rate of 0.1%)[19]. We have not experienced such a problem in over 1000 cases in our daily practice. Mucous discharge, transient light-headedness, dizziness and headache have also been reported in a small number of patients following TNE[18]. TNE should not be attempted in patients with a history of previous nasal trauma, nasal surgery or nasal anatomical problems.

From the endoscopist's perspective, the major limitations of TNE are its narrow working channel and poor suction and air functions when compared to standard endoscopes[48]. In addition, the extreme flexibility of the endoscope may cause difficulty in some manipulations, such as passing through the pylorus. Special biopsy forceps with a diameter of 1.8 mm are required for the working channel. Biopsy samples with these forceps are also smaller but some studies showed no difference in pathological diagnosis of targeted lesions between small and standard diameter forceps[28,49,50]. Nasal scopes have a limited number of available endoscopic accessories and are not appropriate for therapeutic procedures through the working channel. The suction of secretions, gastric content and blood is limited. Thus, TNE is mostly used

Table 2 Advantages and limitations of transnasal endoscopy

Advantages of transnasal endoscopy	Limitations of transnasal endoscopy
More comfortable and tolerable than unsedated TOE	Needs nasal pretreatment
Safer and cost-effective than sedated TOE	Nasal pain and discomfort
Elimination of all side effects due to sedation	Mild epistaxis
Total procedure time is shorter than sedated TOE	Limited functionality (suction, air, water)
No or minimal hemodynamic changes	Extreme flexibility of scope body
No intravenous line is necessary routinely	Narrow working channel. Not appropriate for through the scope interventional procedures
Patient can speak, watch and discuss during procedure	Needs extra training
No need for mouthpiece	No HD image capabilities
Evaluation of nasal cavity, pharynx and larynx	Higher insertion failure rate
Can be done in sitting position	Longer examination time
Visual satisfaction for patients	Not appropriate for patients with nasal problems

TOE: Transoral endoscopy; HD: High-definition.

for diagnostic purposes, except in certain conditions which require a thinner endoscope. The inability of TNE to be used for the delivery of endotherapy due to the small working channel is a true limitation of this method. If it is a planned or likely interventional endoscopy, TOE should be preferred.

There is some controversy about the image capabilities of ultra-thin endoscopes. With improvement in endoscopic technology, ultra-thin scopes with CCD cameras now have good image quality and their field of view is similar to standard endoscopes (Figure 3). Their diagnostic accuracy is nearly the same as standard scopes[25,43,49,51]. However, they do not have high-definition (HD) image capabilities and this may decrease their rate of small lesion detection compared to HD scopes[52,53].

Endoscopists must also receive training in order to perform TNE, particularly those unfamiliar with nasal anatomy. However, in our experience, the learning curve is very short for an experienced endoscopist and they are usually successful at TNE in their first attempts, particularly if under the supervision of a trainer[46].

The failure of endoscopic insertion is greater in TNE when compared to TOE and a 0 to 10% failure rate has been reported previously[25,43,44,54]. In a large study consisting of 1100 patients, the failure rate was 6.1%[44]. In this study, 5.3 and 5.9 mm diameter endoscopes were used and it was reported that the larger endoscope diameter, as well as being female under 35 years old, was predictive for TNE failure. It is important to acknowledge that the failure rate may vary according to patient history, experience of the endoscopist, scope diameter, nasal pretreatment and other potential differences in procedural protocol. Importantly, while insertion failure may be considered a drawback of TNE, it is quite easy to switch to the oral route and this imposes no negative effect on patients. Pharyngeal topical anesthesia during pretreatment makes such a switch easier. In our study, the endoscope insertion failure was 3.5% and the procedure was completed in these patients *via* the oral route without delay.

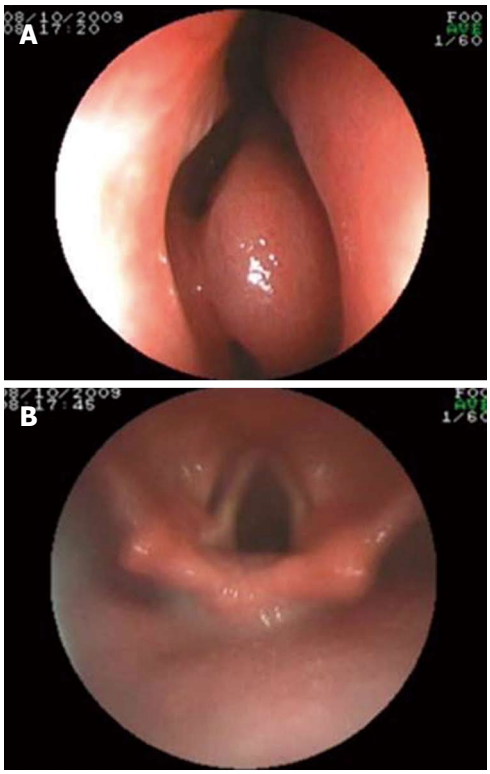

Figure 3 Endoscopic images of transnasal endoscopy during insertion from nose (A) and oropharynx (B).

After pretreatment, the examination time of TNE is usually between 5 and 10 min. It is generally a bit longer than the duration of TOE in clinical studies but this had no impact on the tolerability of the procedure[19,25,26,40,54]. However, when pretreatment and post-procedural monitoring times are taken into consideration, the total time of procedure is shorter for TNE than sedated TOE. Table 2 summarizes the overall advantages and limitations of TNE.

OTHER APPLICATIONS USING ULTRA-THIN ENDOSCOPES

Apart from TNE, ultra-thin endoscopes (UTE) may have some advantages in some special cases due to their thinner diameter, which can be used for interventional purposes by the transnasal or transoral route. The thin diameter of these scopes is an important advantage to pass through gastrointestinal strictures where standard scopes have failed. In a prospective study, our group showed that a 5.9 mm UTE was successful in 49 of 62 patients (79%) with advanced gastrointestinal stricture which standard endoscopes had failed to pass through[55]. In addition to contributing to patient diagnosis, UTE were also used in interventional procedures in 1/3 of those cases. In recent

years, using the advantage of their thin diameter, UTE has been used for different endoscopic therapeutic applications, including nasojejunal feeding tube insertion, percutaneous gastrostomy and jejunostomy, direct cholangioscopy with biopsy and lithotripsy, and a double scope technique for some endoscopic interventions[25,54-60]. These are not discussed in detail here since our focus is to review transnasal endoscopy.

CONCLUSION

TNE is better tolerated than unsedated conventional TOE and offers a more comfortable diagnostic endoscopic procedure to patients. It is safer and less expensive when compared to sedated TOE. Therefore, it should be considered a viable alternative to both unsedated and sedated conventional TOE. Nasal pretreatment is the most important part of TNE to ensure patient tolerance. We believe all endoscopists should be aware of the technical specifications, advantages and limitations of TNE and all eligible patients for TNE should be informed of this method and offered TNE as an alternative to standard oral endoscopy when appropriate. Lastly, the practice of TNE should become a standard part of gastroenterology fellowship training programs to ensure that this procedure becomes part of daily use in endoscopy units.

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MINIREVIEWS

Endoscopic management and prevention of migrated esophageal stents

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Abstract

The use of self-expandable metallic stents has increased recently to palliate inoperable esophageal neoplasia and also in the management of benign strictures. Migration is one of the most common complications after stent placement and the endoscopist should be able to recognize and manage this situation. Several techniques for managing migrated stents have been described, as well as new techniques for preventing stent migration. Most stents have a "lasso" at the upper flange which facilitates stent repositioning or removal. An overtube, endoloop and large polypectomy snare may be useful for the retrieval of stents migrated into the stomach. External fixation of the stent with Shim's technique is efficient in preventing stent migration. Suturing the stent to the esophageal wall, new stent designs with larger flanges and double-layered stents are promising techniques to prevent stent migration but they warrant validation in a larger cohort of patients.

Key words: Endoscopy; Stents; Esophageal cancer; Benign strictures; Complications

Core tip: Migration of self-expandable esophageal stents occurs in up to 36% of cases. The lasso system available in most stents provides a safe way to remove or reposition the stent while it is still in the esophagus. However, when the stent migrates into the stomach, other techniques are needed to guarantee a safer retrieval. The use of clipping, suturing or external fixation should be considered for stents at high risk for migration.

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INTRODUCTION

Placement of an esophageal self-expandable stent is a safe and effective procedure to palliate inoperable esophageal carcinoma. Recently, it also has been indicated for the management of benign strictures recalcitrant to endoscopic dilation[1-4].

Migration is one of the most common complications after stent placement, ranging from 4%-36%[5-11].

Although the majority of migrations are asymptomatic, symptoms like recurrent dysphagia and chest pain may arise. A foreign body sensation may be present in cases of proximal dislodgment. Fully covered stents, plastic stents, concurrent chemotherapy and/or radiotherapy and stents placed across the gastroesophageal junction are factors that increase the risk of migration[4,5,12,13].

Management of migrated stents is a controversial issue[14] and it is extremely important that the endoscopist is able to recognize and manage this situation. In this review, we will discuss how to manage stent migration, as well as the endoscopic techniques that can be used for retrieving migrated stents and the new techniques for preventing migration.

CONSERVATIVE APPROACH TO DISTALLY MIGRATED ESOPHAGEAL STENTS

Some authors recommend conservative management of migrated esophageal stents. De Palma *et al*[15] described 13 cases of esophageal stents migrated to the stomach. Three patients eliminated the stent through the rectum, one underwent surgery for stent impaction in the colon, and in nine patients, the stents remained in the stomach without clinical complications (range, 1.8-6.5 mo). Di Fiore *et al*[16] described two cases of stent impaction in the duodenum that could not be resolved by endoscopy. The stents were left in place and the patients died of metastatic disease 2 and 10 mo later, respectively. Williams *et al*[17] related a case of esophageal stent migration to the colon, with the patient presenting with constipation which was resolved conservatively. Indeed, migration of an esophageal stent to the stomach should not be considered an emergency but small bowel obstruction and perforation can occur[18-22], so migrated stents should be removed whenever possible.

ENDOSCOPIC REMOVAL

Endoscopic removal will depend on the kind of stent and the site of migration. When the metallic stent is distally migrated but still in the esophagus, those with a proximal lasso can be pulled back by grasping the lasso with rat-tooth forceps, which allows constriction of the upper flange, permitting repositioning or removal. Endoscopic traction of plastic or metallic stents that do not have a proximal lasso might be trickier. A double-channel endoscope can be helpful for grasping both sides of the upper flange and pulling the stent. In this situation, previous endoscopic dilation is advisable if a proximal stricture is present.

A more challenging situation is when a stent migrates to the stomach. Metallic stents with a proximal lasso can be removed by grabbing and pulling the lasso. However, in some cases, constriction is not enough to remove the stent without esophageal injury, especially if a stenotic tumor is present. Some techniques have been developed to deal with this situation: (1) Endoloops: one or more endoloops may be placed to reduce the size of the stent and facilitate its removal[23,24]; (2) Polypectomy snare: one of the flanges of the stent can be grasped with a polypectomy snare, reducing the proximal diameter and making stent removal possible[25]. Some variations of this technique have been described when collapsing the stent proves to be difficult. One example is the use of a snare and rat-tooth forceps passed through a double-channel endoscope. The forceps is passed through the snare, which is advanced along the forceps and closed, grasping the stent[26]. Another technique variation is the replacement of the plastic sheath of the snare by a metallic sheath from a basket designed for bile duct stone lithotripsy[27]. The stiffness of the metallic sheath facilitates the collapsing of the stent by the snare; (3) "Push and grasper" technique: a biliary stent pusher (10 Fr for double-channel and 7 Fr for standard endoscope) is inserted into the operational channel and a grasp forceps is passed inside the pusher (pediatric, 7 Fr pusher) (Figure 1). The lasso is grasped and pulled back into the pusher while the pusher is advanced against the stent. This maneuver allows constraining of the proximal flange of the stent, facilitating its removal[28]; (4) A foreign body hood protector in combination with a rat-tooth forceps or snare can be used to facilitate the removal of the stent, reducing the risk of mucosa injury during removal[29]; (5) An overtube may be used to protect the esophageal mucosa while retrieving the stent with a rat-tooth grasper[30].

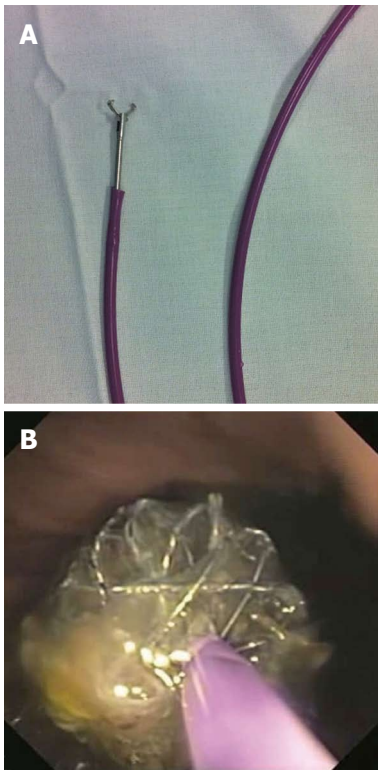

Figure 1 Endoscopic removal. A: Rat-toothed grasper inside the biliary stent pusher; B: Stent border constrained by the grasper and pusher together.

Figure 2 The Niti-S stent has a double-layered configuration. The inner covered layer protects against tumor ingrowth and the additional uncovered mesh helps to resist migration.

Enteroscopy can be used to attempt removal of a stent migrated beyond the duodenum. Kohli *et al*[31] described the use of double-balloon enteroscopy to retrieve a self expandable plastic esophageal stent migrated through a Roux-en-Y anastomosis into the distal small intestine. In general, stents migrated beyond the reach of an endoscope should be observed with serial radiographs and physical examination.

PREVENTING ESOPHAGEAL STENT MIGRATION

Use of larger diameter stents (25-28 mm) may reduce the risk of migration, as suggested by two studies with migration rates varying from 8%-15%[32,33]. However, larger stents can increase the risk of stent-related complications involving the esophagus, such as hemorrhage, perforation and fistula[33-35].

New stent designs were developed with the intent to reduce migration. The Niti-S stent (Taewong Medical, Seoul, South Korea) has a double layer configuration, with an inner polyurethane layer to prevent tumor ingrowth and an outer uncovered nitinol-wire mesh, which was designed to embed into the esophageal wall and reduce migration (Figure 2). In a study with 42 patients, Verschuur *et al*[36] demonstrated low migration (7%) and ingrowth rates (5%) with this stent. In a series with 48 patients, Kim *et al*[37] showed a low migration rate (2%), but a high stent dysfunction rate caused by tumor overgrowth (27.1%). Another novel design, fully covered metal stent (Hanarostent Skidpoof; M.I. Tech Co, Pyeongtaek, South Korea) was described by Ji *et al*[38]. This stent has multiple protuberances on its body designed to be separate from the inner silicone membrane so that they can embed into the mucosa. The authors compared the new stent with a regular fully covered stent in dogs and showed a lower migration rate with the new stent (100% *vs* 55%, P = 0.035).

Some techniques of stent fixation have been described preventing migration. Shim's technique consists of a modified covered metallic stent designed with a silk thread attached at the edge of the proximal end of the stent (Hanarostent™; M.I. Tech Co, Pyeongtaek, South Korea). After stent deployment, the thread is fixed to the patient's nose or ear lobe by tape. The stent also has a proximal uncovered flange that allows tissue embedment. Endoscopy is repeated 2 wk after fixation and, if the stent is embedded in the esophageal mucosa and does not separate from the esophagus with air insufflation, the external fixation is removed. Using this technique, Shim *et al*[39] reported no migration in 61 patients. If stents with Shim's technique are not available, a modified technique can be used[40]. A length of dental floss or equivalent thread is grasped with a biopsy forceps and passed through the working channel of a standard endoscope

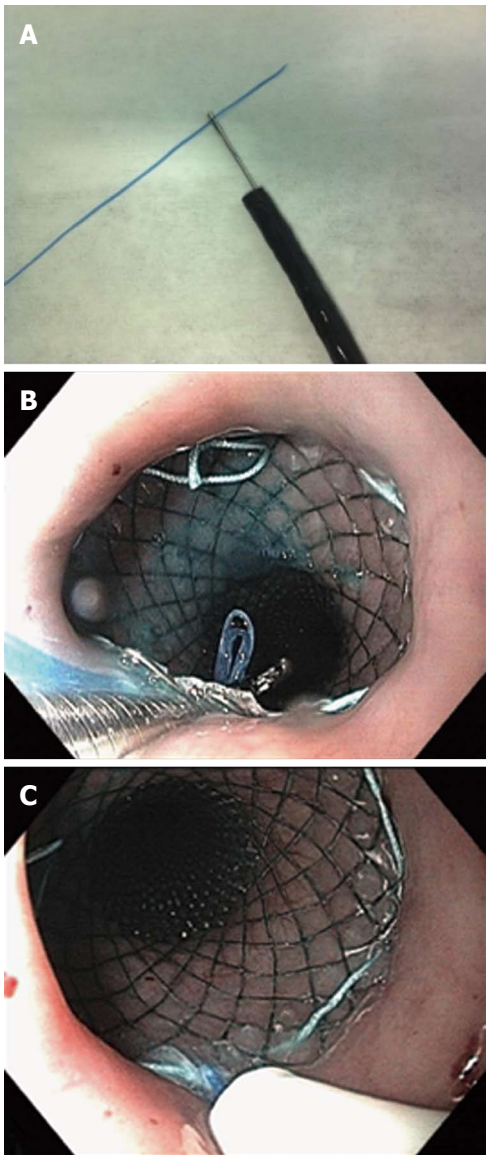

Figure 3 A length of dental floss or equivalent thread is grasped with a biopsy forceps and passed through the working channel of a standard endoscope. A: The dental floss is grasped with a biopsy forceps; B: The dental floss is passed through the stent mesh from the outside to the inside and carried down using the biopsy forceps; C: The dental floss is inserted into a nasoenteral tube, which is pushed down towards the mesh to protect the nasopharyngeal mucosa.

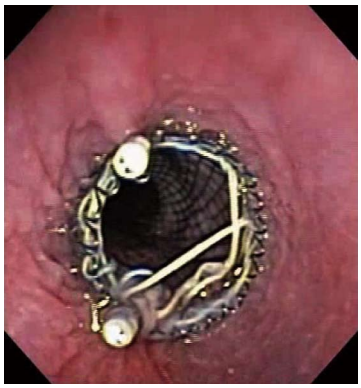

Figure 4 Endoscopic clips may be applied at the upper border of the stent to prevent migration.

(Figure 3). The endoscope is positioned at the upper border of the stent and the forceps is passed through the stent mesh from outside to inside and advanced, carrying down the floss. The forceps is retrieved, leaving the floss down at the stent. The endoscope is advanced through the stent and the floss is grasped and gently brought back to the mouth, avoiding stent dislodgment. The floss is passed inside a nasoenteric soft tube to protect the nasopharyngeal mucosa. In addition to the silk and dental floss technique, other external stent fixation devices described have included umbilical tape[41] and snare[42].

Fixation of the proximal flare of the stent to the esophageal mucosa with clips may be useful to avoid stent migration (Figure 4). Kato *et al*[43] reported no migration in nine patients with stent fixation with clips (three with strictures and six with digestive-respiratory fistula). In a series of 44 patients, fixation of the upper flare end of the stent to the esophageal mucosa with clips reduced migration rates of fully covered stents from 34% to 13% (3 out of 23 patients)[44].

Recently, a small pilot study described successful stent fixation using an overstitch endoscopic suturing device (Apollo Endosurgery, Inc., Austin, TX, United States). This device can make interrupted or continuous stitches of various lengths and each stitch is finished with intracorporeal knot tying[45].

CONCLUSION

Esophageal stent placement is a safe and effective procedure to palliate dysphagia in patients with esophageal cancer, as well as to treat benign conditions such as esophageal strictures, fistulas and perforation. Migration is the most common complication after stent placement, especially with fully covered stents, but can be prevented by adequate stent selection and external or internal stent fixation. Migrated stents should be removed or repositioned whenever possible. Constriction of the proximal flare is the most important step for stent removal and forceps, snare and loops can be used individually or in combination to achieve adequate constriction. Endoscopic removal of the migrated stent is a low-morbidity procedure.

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BRIEF ARTICLE

An automated spring-loaded needle for endoscopic ultrasound-guided abdominal paracentesis in cancer patients

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Abstract

AIM: To evaluate the feasibility of using an automated spring-loaded needle device for endoscopic ultrasound (EUS)-guided abdominal paracentesis (EUS-P) to see if this would make it easier to puncture the mobile and lax gastric wall for EUS-P.

METHODS: The EUS database and electronic medical records at Fukushima Medical University Hospital were searched from January 2001 to April 2011. Patients with a history of cancer and who underwent EUS-P using an automated spring-loaded needle device with a 22-gauge puncture needle were included. The needle was passed through the instrument channel and advanced through the gastrointestinal wall under EUS guidance into the echo-free space in the abdominal cavity and ascitic fluid was collected. The confirmed diagnosis of malignant ascites included positive cytology and results from careful clinical observation for at least 6 mo in patients with negative cytology. The technical success rate, cytology results and complications were evaluated.

RESULTS: We found 11 patients who underwent EUS-P with an automated spring-loaded needle device. In 4 cases, ascites was revealed only with EUS but not in other imaging modalities. EUS-P was done in 7 other cases because there was minimal ascitic fluid and no safe window for percutaneous abdominal aspiration. Ascitic fluid was obtained in all cases by EUS-P. The average amount aspirated was 14.1 mL (range 0.5-38 mL) and that was sent for cytological exam. The etiology of ascitic fluid was benign in 5 patients and malignant in 6. In all cases, ascitic fluid was obtained with the first needle pass. No procedure-related adverse effects occurred.

CONCLUSION: EUS-P with an automated spring-loaded needle device is a feasible and safe method for

ascites evaluation.

Key words: Ascetic fluid; Malignancy; Endoscopic ultrasound; Paracentesis; Fine needle aspiration

Core tip: Even in patients with a minute amount of ascitic fluid, an automated spring-loaded needle device enabled us to perform endoscopic ultrasound (EUS)-guided abdominal paracentesis (EUS-P) readily, which has the potential to play an important role for staging of cancer since the establishment of malignant ascites denotes a more advanced stage of cancer.

Suzuki R, Irisawa A, Bhutani MS, Hikichi T, Takagi T, Shibukawa G, Sato A, Sato M, Ikeda T, Watanabe K, Nakamura J, Annangi S, Tasaki K, Obara K, Ohira H. An automated spring-loaded needle for endoscopic ultrasound-guided abdominal paracentesis in cancer patients. *World J Gastrointest Endosc* 2014; 6(2): 55-59 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i2/55.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i2.55

INTRODUCTION

The existence of malignant ascites in cancer patients indicates a dismal prognosis[1-9]. Therefore, the etiology of ascitic fluid in cancer patients needs careful evaluation. Endoscopic ultrasound (EUS) can detect a minute or minimal amount of ascitic fluid that may be undetectable in other imaging modalities, including abdominal ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI)[10-15]. Moreover, EUS-guided abdominal paracentesis (EUS-P) has the potential to play an important role for staging of cancer since the establishment of malignant ascites denotes a more advanced stage of cancer[16-20]. Although EUS-P is a useful technique at times, we encountered technical difficulties during EUS-P, probably due to less counteracting force from extramural objects and a lax gastrointestinal wall.

An automated spring-loaded needle device which was designed to function analogously to spring-loaded biopsy needles used for percutaneous tissue sampling with high puncture speed was developed by Binmoeller *et al*[21,22] for cases in which penetration during EUS-FNA is difficult[23,24].

In this study, we aimed to evaluate the feasibility of using an automated spring-loaded needle device for EUS-P to see if this would make it easier to puncture the mobile and lax gastric wall for EUS-P.

MATERIALS AND METHODS

The EUS database and electronic records at Fukushima Medical University were searched from January 2001 to April 2011 for patients with a history of cancer and for whom EUS-P was performed using an automated spring-loaded needle device. Before EUS-P, written informed consent was obtained from all patients. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review committee.

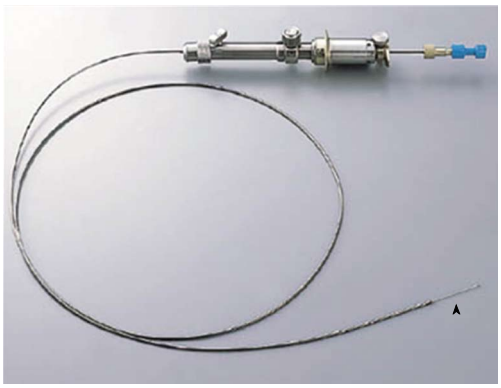

Figure 1 An automated spring-loaded needle device (NA-11J-KB; Olympus Medical Systems, Tokyo, Japan) with 22-gauge puncture needle. Arrowhead indicates the needle tip.

Materials and technique

EUS-P was performed using a curved linear-array echoendoscope (GF-UCT240-AL5 or GF-UC240P-AL5; Olympus Medical Systems Corp., Tokyo, Japan) in conjunction with SSD-5500 (Aloka Co. Ltd., Tokyo, Japan), or using a FG-36UX (Pentax Corp., Tokyo, Japan) in conjunction with EUB-6000 (Hitachi Ltd., Tokyo, Japan). The needle device in all patients was an automated spring-loaded powershot needle (NA-11J-KB; Olympus Medical Systems Corp., Tokyo, Japan) with a 22-gauge puncture needle (Figure 1). In patients in whom EUS-FNA was performed for other lesions, EUS-P was initially performed to prevent potential seeding or dissemination and needles were changed to prevent contamination after this procedure.

Ascitic fluid was defined as the presence of extraluminal free fluid (anechoic space on EUS), as viewed from the stomach or duodenum. The needle was passed through the instrument channel and advanced through the gastrointestinal (GI) wall under EUS guidance into the echo-free space in the abdominal cavity (Figure 2). In patients with GI lesions, puncture points were determined carefully to avoid tissue contamination from primary lesions. After being guided into the target lesion, the stylet was removed. The needle was retracted to maintain its position within the fluid and avoid sucking up against adjacent bowel and/or omentum while aspirating. Subsequently, the suction syringe was released and the needle was withdrawn into the catheter. It was then removed completely. Aspirated ascitic fluid was sprayed on the glass slide or in the tube and submitted for pathological examination.

The cytological criteria used for reporting EUS-P

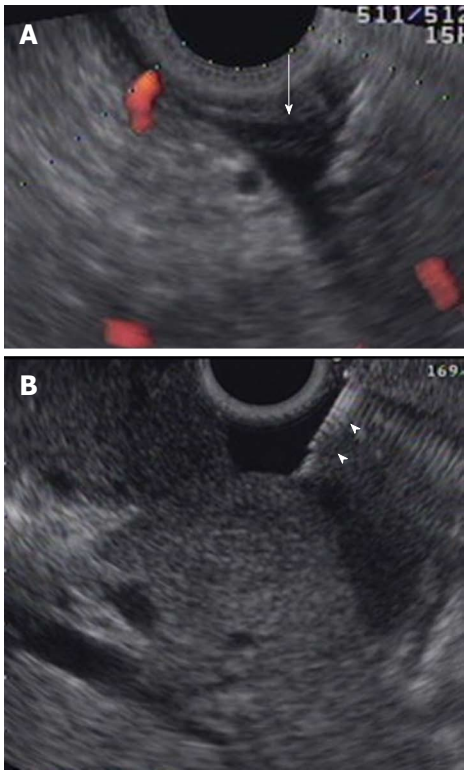

Figure 2 Endoscopic ultrasound-guided abdominal paracentesis. A: A small amount ascites was detected as the echo-free space around the stomach (arrow); B: Endoscopic ultrasound-guided abdominal paracentesis was performed. Endoscopic ultrasound image illustrating needle position (arrow head).

results were based on the guidelines of the Papanicolaou Society of Cytopathology for fine needle aspiration and reporting. We regarded Class Ⅰ-Ⅱ as benign, Class Ⅲ as atypical/indeterminate, and Class Ⅳ/Ⅴ as malignant[25].

The confirmed diagnosis of malignant ascites included positive cytology and results from careful clinical observation for at least 6 mo in patients with negative cytology.

RESULTS

Eleven patients (7 males and 4 females) were enrolled. The average age of patients was 66.4 years (range 50-78 years). Primary malignancy was pancreatic adenocarcinoma in 6 patients, cholangiocarcinoma in 2 patients, and breast cancer, gastric cancer and malignant lymphoma in 1 patient, respectively. Six patients with pancreatic adenocarcinoma underwent EUS-FNA for primary lesions at the same time of EUS-P. In 4 others with synchronous malignancy, primary lesions were diagnosed with other modalities (*e.g.*, endoscopic retrograde cholangiopancreatography, endoscopy). In one patient with a history of breast cancer 5 years prior to EUS-P, concomitant malignancy was not detected. The clinical characteristics are summarized in Table 1.

Diagnostic value

Ascitic fluid was obtained in all patients. The average amount was 14.1 mL (range 0.5-38 mL). The etiology of ascitic fluid was benign in 5 patients and malignant in 6. Among these 11 patients, ascitic fluid was revealed with US or CT in 63.6% (7 out of 11 patients) but there was no appropriate percutaneous route for image-guided abdominal paracentesis. By contrast, in 4 other patients (36.4%), ascites was detected with only EUS. EUS-FNA was performed for pancreatic mass lesions in all these patients and ascites was an incidental finding. The average amount of ascites obtained with EUS-P was only 2.6 mL (range 0.5-5 mL) in these patients. No complications occurred in any of these procedures.

Table 1 Patients underwent endoscopic ultrasound-guided abdominal paracentesis

Patient	Age (yr)/ sex	Primary malignancy	Aspirated ascitic fluid (mL)	Ascitic fluid in US/CT/ MRI	Malignant ascitic fluid
1	64/M	ML	38	+	-
2	50/M	PDAC	20	+	+
3	78/F	CC	6	+	-
4	70/M	PDAC	0.5	-	+
5	76/ M	GC, LC	15	+	-
6	55/M	PDAC	2	-	+
7	62/F	CC	25	+	+
8	77/M	PDAC	10	+	-
9	66/F	BC	30	+	+
10	70/F	PDAC	3	-	+
11	63/M	PDAC	5	-	-

EUS-P: Endoscopic ultrasound-guided abdominal paracentesis; M: Male; F: Female; ML: Malignant lymphoma; PDAC: Pancreatic ductal adenocarcinoma; CC: Cholangiocarcinoma; GC: Gastric cancer; LC: Lung cancer; BC: Breast cancer; US: Ultrasound; CT: Computed tomography; MRI: Magnetic resonance imaging.

DISCUSSION

Our results show that EUS-P with an automated spring-loaded needle device can be a useful technique to obtain a minute amount of ascitic fluid in cancer patients. Furthermore, EUS showed its ability to detect a scant amount of ascitic fluid which US and CT could not detect in 4 patients with pancreatic ductal adenocarcinoma. In these patients, the amount of aspirated fluid was only 2.6 mL on average. Two of them were diagnosed as malignant and this result changed their management.

Regarding the technical aspects, it is sometimes difficult to penetrate the mobile and lax gastrointestinal wall with a standard EUS-FNA needle. It may be a greater problem in patients who require EUS-P because there is less counteracting force from extramural objects. To solve this problem, we aimed to evaluate the feasibility of using an automated spring-loaded needle device with high puncture speed for EUS-P and to show its high technical success rate to obtain a minimum amount of ascitic fluid[21-24]. Limitations of our study were that it was retrospective and had a small number of cases. Additionally, with the lack of a control group with a standard EUS-FNA needle, we were unable to conclude which was the

optimal type of needle for EUS-P.

Otherwise, based on our experience, we conclude that both EUS and EUS-P are useful in the management of cancer patients with gastrointestinal or other malignancies to detect and aspirate minute/minimal amounts of ascites that may not be visible by other imaging modalities or when percutaneous aspiration may not be feasible due to minimal fluid and lack of a suitable path. The automated spring-loaded needle device may provide a technical advantage, especially in cases that are difficult to penetrate the lax and mobile gastrointestinal wall.

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COMMENTS

Background

The etiology of ascitic fluid in cancer patients needs careful evaluation. Since the authors sometimes have difficulties in the detection and sampling of small amounts of ascitic fluid, the ability of endoscopic ultrasound (EUS) and EUS-guided abdominal paracentesis (EUS-P) has the potential to play an important role for staging of cancer. Although EUS-P is a useful technique at times, the authors encountered technical difficulties during EUS-P, probably due to less counteracting force from extramural objects and a lax gastrointestinal wall.

Research frontiers

The importance of EUS-P for cancer staging has not been well recognized yet. Regarding the technical aspects, it is sometimes difficult to penetrate the mobile and lax gastrointestinal wall with a standard EUS-FNA needle. It may be a greater problem in patients who require EUS-P because there is less counteracting force from extramural objects.

Innovations and breakthroughs

The authors aimed to evaluate the feasibility of using an automated spring-loaded needle device with high puncture speed for EUS-P and to show its high technical success rate to obtain minimum amount of ascitic fluid.

Applications

This method can be useful in every patient with ascites who requires cancer staging to determine their treatment strategy.

Terminology

EUS: a medical procedure in which endoscopy is combined with ultrasound to obtain images of the internal organs in the chest and abdomen. Paracentesis: a form of body fluid sampling procedure in which the peritoneal cavity is punctured by a needle to sample peritoneal fluid.

Peer review

The results show that EUS-P with an automated spring-loaded needle device can be a useful technique to obtain a minute amount of ascitic fluid in cancer patients. The article is interesting, unique and worthy of publication.

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Minireview on laparoscopic hepatobiliary and pancreatic surgery

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Abstract

The first laparoscopic cholecystectomy was performed in the mid-1980s. Since then, laparoscopic surgery has continued to gain prominence in numerous fields, and has, in some fields, replaced open surgery as the preferred operative technique. The role of laparoscopy in staging cancer is controversial, with regards to gallbladder carcinoma, pancreatic carcinoma, hepatocellular carcinoma and liver metastasis from colorectal carcinoma, laparoscopy in conjunction with intraoperative ultrasound has prevented nontherapeutic operations, and facilitated therapeutic operations. Laparoscopic cholecystectomy is the preferred option in the management of gallbladder disease. Meta-analyses comparing laparoscopic to open distal pancreatectomy show that laparoscopic pancreatectomy is safe and efficacious in the management of benign and malignant disease, and have better patient outcomes. A pancreaticoduodenectomy is a more complex operation and the laparoscopic technique is not feasible for this operation at this time. Robotic assisted pancreaticoduodenectomy has been tried with limited success at this time, but with continuing advancement in this field, this operation would eventually be feasible. Liver resection remains to be the best management for hepatocellular carcinoma, cholangiocarcinoma and colorectal liver metastases. Systematic reviews and meta-analyses have shown that laparoscopic liver resections result in patients with equal or less blood loss and shorter hospital stays, as compared to open surgery. With improving equipment and technique, and the incorporation of robotic surgery, minimally invasive liver resection operative times will improve and be more efficacious. With the incorporation of robotic surgery into hepatobiliary surgery, donor hepatectomies have also been completed with success. The management of benign and malignant disease with minimally invasive hepatobiliary and pancreatic surgery is safe and efficacious.

Key words: Laparoscopic; Liver resection; Pancreatectomy; Cholecystectomy; Pancreaticoduodenectomy; Cancer; Tumour

Core tip: This minireview presents the importance of laparoscopy in facilitating laparoscopic hepatobiliary and pancreatic surgery, and the efficacy and safety of laparoscopic hepatobiliary and pancreatic surgery. Laparoscopic surgery is the preferred management of benign and malignant disease for selected patients. The advantages include confirmation of diagnosis, prevention of nontherapeutic operations, decreased hospital stay and better post-operative function and cosmetic outcome. Meta-analyses demonstrate that laparoscopic liver resections, pancreatectomies and cholecystectomies are efficacious. There is less blood loss; the hospital stays are shorter with laparoscopic surgeries. There is no compromise to the oncological resection margins when compared to open surgery. Laparoscopic surgery is safe and efficacious in the management of benign and malignant hepatobiliary and pancreatic diseases.

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LAPAROSCOPY

Pancreas

Pancreatic cancer carries a poor prognosis with a 5-year relative survival rate of 5.8% (SEER Stat Fact Sheets: Pancreas). At least 80% of patients with pancreatic cancer present with either locally advanced or metastatic disease and are not resectable at the time of diagnosis[1]. Complete surgical resection is the only curative treatment with potential for long-term survival[2]. Accurate staging is essential in treatment planning and in determining appropriate management of patients with pancreatic cancer by selecting patients who can benefit from surgery and identifying patients with non-resectable disease to avoid non-therapeutic laparotomies[3].

Up to one third of patients with high-quality preoperative imaging will have radiographically occult distant metastatic or locally unresectable disease at the time of staging laparoscopy[2]. In pancreatic adenocarcinoma, laparoscopic staging allows for the identification of subradiographic metastatic disease in 10%-15% of patients with radiographically resectable cancer, and in approximately 30% of patients with locally advanced disease[2]. Staging laparoscopy is associated with decreased length of stay, reduced postoperative pain, and a higher likelihood of receiving systemic therapy compared to laparotomy without significantly increasing operative time[2,4,5].

However, advances in imaging technology have decreased the yield of staging laparoscopy over time. Multiphase, multidetector thin-slide computed tomography (CT) scans produce high-resolution images providing details about local vascular involvement and distant metastatic disease[6]. Endoscopic ultrasound (EUS) is also being increasingly used to image the tumor and its relationship to adjacent structures and to obtain biopsies of pancreatic lesions and regional lymph nodes[6]. A study by White *et al*[7] evaluated 1045 patients from a prospective database who underwent staging laparoscopy for radiographically resectable pancreatic and peripancreatic tumors over a 10 year period from 1995 to 2005 to examine the yield of staging laparoscopy. The study reports that the yield of laparoscopy has diminished over the 10 year period and exceeds 10% only for patients with pancreatic adenocarcinoma[7].

The use of staging laparoscopy in pancreatic cancer remains controversial. Whether staging laparoscopy should be used routinely or only in selected cases is a matter of debate. Studies suggest that staging laparoscopy should be reserved for selected cases where the yield is likely to justify the additional procedural risk and cost. Studies recommend that patients with tumours larger than three centimeters, tumours in the neck, body or tail, or patients with equivocal CT scan findings for metastatic disease, may benefit from laparoscopy[8,9].

Gallbladder

Gallbladder carcinoma is a rare malignancy and the incidence of intra or post-operative diagnosis is between 0.2% to 2.8%. Due to an increase in laparoscopic cholecystectomies, incidental finding of gallbladder cancer has also increased[10]. The best management for gallbladder carcinoma is surgical resection: a resection with malignancy negative margins (R0 resection). In a T3 to T4 gallbladder carcinoma, an R0 resection would result in a 26% 5-year survival rate, as compared to a 9% survival rate in a less than R0 resection[11]. If gallbladder carcinoma is suspected on imaging, the role of laparoscopic staging for gallbladder carcinoma has been shown to be sensitive in detecting unresectable disease and diseased lesions. The evidence supports that staging laparoscopy does not impact on overall survival, and prevents patients with unresectable disease from a nontherapeutic laparotomy[12]. The use of a laparoscopic ultrasound as an adjunct to laparoscopy further increases the accuracy and specificity of diagnosis and staging[13]. A retrospective review completed by Ferrarese *et al*[10], further re-enforces the role of meticulous peri-operative diagnosis, intraoperative staging and cholecystectomy in preventing unnecessary laparotomies, and identify the patients who will benefit from a resection.

Liver

This section discusses the importance of laparoscopy and the role of laparoscopic ultrasound in confirming the diagnosis and planning the liver resection or ablation.

Laparoscopy is particularly useful in cases when resectability is uncertain prior to surgery. Jarnagin *et al*[4] examined the benefits of preoperative laparoscopy in patients with colorectal metastasis (CRM), and identified five factors that may predict the presence of occult intrahepatic or extrahepatic disease that may make patients unresectable. These factors are the presence of more than one liver tumor, positive node status of primary tumor, disease-free interval of less than 1 year, presence of liver tumor that is larger than 5 cm and carcinoembryonic antigen (CEA) level greater than 200 ng/mL. If any patient has more than 2 of these factors, 42% of the time would have occult disease rendering them unresectable.

Accurate staging of intrahepatic cholangiocarcinoma (IHC) is just as important, as complete resection offers the best long-term survival. Patients with large lesions, positive nodes or multifocal IHC do not benefit from resection[14]. An adjunct to staging laparoscopy is the laparoscopic ultrasound. The laparoscopic ultrasound is sensitive in detecting parenchymal liver lesions[15]. Because of this, the routine use of laparoscopy with concomitant laparoscopic ultrasound can save patients from unnecessary laparotomy[4,14].

If a patient with hepatocellular carcinoma (HCC) is not eligible for liver resection, there are other multimodal

approaches to manage HCC primarily or in conjunction with liver resection or a bridge to transplantation: local ablation with alcohol or radio frequency, chemoembolization, and radioembolization[16]. The laparoscopic ultrasound is useful in these cases as it allows precise examination of these lesions and the surrounding vessels, and facilitates ultrasound-guided ablation of HCC.

PANCREAS

This section will focus on the role of laparoscopic distal pancreatectomy and pancreaticoduodenectomy, and the alternatives to management of unresectable biliary and duodenal obstructive cancers.

Distal pancreatectomy

Report of the first laparoscopic distal pancreatectomy (LDP) was in 1996[17,18]. Subsequent studies have demonstrated that laparoscopic distal pancreatectomy is as safe as open distal pancreatectomy[19]. It is now increasingly performed as the better alternate approach for distal pancreatectomy in selected patients. Two meta-analyses further support that laparoscopic distal pancreatectomy is associated with a significantly lower blood loss and reduced length of stay as compared to open distal pancreatectomy (ODP)[20,21]. In addition, the Meta-analysis completed by Venkat *et al*[20] combined four retrospective studies to show that there is no difference in margin positivity between LDP and ODP, but there are more lymph nodes harvested in ODP than LDP. A retrospective study completed by Magge *et al*[22] compared 62 consecutive patients undergoing ODP or minimally invasive distal pancreatectomy (MIDP), and found the medial lymph node clearance is similar (OPD 12 and MIDP 11) and demonstrate that the rate of pancreatic fistula (ODP 29% and MIDP 21%), and the overall survival after ODP or intended MIDP was equivalent after adjusting for comorbidity and year of surgery.

The rate of postoperative complications after LDP and ODP are similar or less in the LDP group. Nakamura and Nakashima demonstrate this in a meta-analysis. The overall morbidity is significantly lower in the LDP group, and there is no significant difference in mortality. The pancreatic fistula and wound infection rates are significantly lower in the LDP than in ODP groups [OR = 0.34/0.46, 95%CI: (0.20-0.57)/(0.23-0.91); $P < 0.0001$/$P = 0.03$]. A more recent retrospective American study also has similar findings[23,24]. The estimated blood loss is less and the need for blood transfusion is less in the LDP group. Interestingly, the rates of grade B and C pancreatic fistulas are also less in the LDP group.

Despite all the current medical advancement, the incidence of pancreatic fistula associated with ODP and LDP can be as high as 30%. The following are some factors and techniques, which have been proposed to lower this rate. Meta-analysis comparing staple *vs* suture closure of pancreatic remnant after distal pancreatectomy demonstrated no difference[25]. The use of fibrin glue adhesive sealing may prevent postoperative pancreatic fistula formation[26,27]. A single-blinded, randomized control trial, and subsequent meta-analysis and studies demonstrate that mesh re-enforcement (either with bovine pericardium, Seamguard or Peristrips Dry) decreases the rate of pancreatic fistula formation compared to bare metal staple lines[28]. This has been challenged, as the use of Seamguard may increase leaks[29]. In these studies, thick pancreases were excluded from these studies. Eguchi *et al*[30] demonstrate that the thick pancreas is an independent risk factor for pancreatic fistula formation, and the stapler should be reserved for thin pancreas. The authors suggest that thick pancreas should be over sewn.

Konstantinidis *et al*[31] reviewed 1705 patient from a clinic pathologic database for pancreatic cancer and identified that patients undergoing R1 resection still have an improved survival compared with patients with locally advanced unresectable pancreatic adenocarcinoma. R0 resections have an improved survival compared with R1 resections, but this survival benefit is lost when the tumor is within 1 mm of the resection margin. Meta-analysis and numerous study demonstrate that the oncological resection margin between LDP and ODP are similar, making LDP a suitable option for the management of pancreatic cancers of the body and tail in selected patients[32].

The local recurrence of pancreatic cancer is 80% within 2 years after resection with curative intent. Encouraging results from Germany suggest that resection of locally recurring pancreatic cancer is feasible, safe and associated with an improved survival outcome. They evaluated 97 patients from 2001 to 2009, and found that patients with isolated local recurrence who underwent an R0 resection had a median survival of 30.5 mo[33]. Perhaps the use of laparoscopic surgery may decrease the adhesion formation and facilitate re-do operations.

Controversy still remains over whether small PNET need to be excised or treated non-operatively[32]. The management of PNET if it is larger than 2 cm, growing, functional or associated with the pancreatic duct, should be resected. A meta-analysis comparing 906 patients with PNET of who 22% underwent LPS and 78% underwent OPS, demonstrated that there is no difference in pancreatic fistula development, operative time or mortality. LPS for PNET is safe and associated with shorter length of stay than OPS[34].

It was thought that LPD for the management of pancreatic malignancies should be managed in high-volume tertiary referral centers. A retrospective study demonstrates that LDP can be safely and effectively performed by any surgeon comfortable with laparoscopic techniques, and may not require specialized training or a special center, however, the authors also imply that further data are required to make more definitive conclusions[35].

With the exception of the systemic review and meta-analysis completed by Jin *et al*[21], most studies demonstrate that the operative time in LDP is significantly longer than in ODP. This is most likely due to a selection bias and an inherent learning curve associated with this

procedure. Interestingly, there is a clockwise technique developed by Asbun and Stauffer, which may be a superior technique with regards to, decreased operative time (182 min), relatively similar pancreatic fistula formation, larger lymph node harvest (14 nodes), and acceptable oncological (negative margins) resection quality. This series (n = 28) will need more surgeons to validate the reliable and safe five-step method[36].

Robot-assisted minimally invasive distal pancreatectomy has been shown to be superior to laparoscopic distal pancreatectomy. It is equivalent to LDPs outcome and safety, and there is a significant reduction in conversion to open resection. As the result, the recovery time is faster. In addition, there is a reduced risk of excessive blood loss, improved lymph node yield, and higher rates of margin negative resections compared to LDP[37,38]. This is most likely due to the larger field of view. With this in mind, perhaps robotic assisted surgery would be the better operative tool for malignant disease in the future.

Pancreaticoduodenectomy

Laparoscopic pancreaticoduodenectomy (LPD) was first reported in 1994[18]. The cost analysis of an open pancreaticoduodenectomy (OPD) and LPD are equivalent. While operating time and supply costs are higher for LPD, this is balanced by decreased cost of the postoperative admission[39].

There are several advantages robotic surgery has over laparoscopic surgery that make it more feasible to complete complex procedures. Although there is a learning curve, there is a larger surgical field than in laparoscopic surgery. A systematic review on robotic pancreaticoduodenectomy completed by an Italian group found that the rate of conversion was 14%, and the overall morbidity rate was reoperation rate was 7.3%[40]. Data on cost analysis is lacking and further studies are needed to evaluate also the cost-effectiveness of the robotic approach.

Unresectable cancer causing obstruction

It is unclear as to the best management of patients with biliary and duodenal obstruction secondary to malignancy. Multiple systemic reviews have been completed to further determine the best options for these patients.

A meta-analysis of randomized trials comparing immediate stent placement to surgical bypass in the management of unresectable pancreatic and peripancreatic cancer in 379 patients conclude that nearly all patients would benefit from some procedure to manage biliary obstructions, but in patients with low surgical risk, they benefit more from surgery because the risk of recurrence and subsequent hospital utilization was lower than patients with stents[41]. Although the initial postoperative stay is longer, patient with surgical bypass have significantly longer symptom free survival and fewer hospital readmissions[42]. They recommend that patients with unresectable disease on exploratory laparotomy and those with no evidence of metastasis are candidates for operative bypass as they have a longer disease survival. Other groups have not shown much difference between a gastrojejunostomy and stent[43].

Duodenal and biliary stents are 90% successful with low morbidity, and compared to surgery, lower initial cost and better quality of life[44]. With the use of expandable stents, the quality of life and hospital visits should improve. According to the SUSTENT study, when they compared the medical effects, quality of life and cost of surgical gastrojejunostomy or endoscopic stent placement for palliation, they demonstrate that despite slow initial symptom improvement, a gastrojejunostomy had better long-term results. Therefore, they also conclude that the surgical gastrojejunostomy is the better option for patients with life expectancy longer than 2 mo, and a stent is preferred for those patients with less than 2 mo life expectancy, as it has better short-term results[45,46]. A group from China has reported laparoscopic roux-en-y cholangiojejunostomy in 103 patients with good outcomes. Patients with metastatic disease died from cancer, and not postoperative complications. Their complication rate was less than 5%[47].

Endoscopic management of biliary and duodenal obstructions is an option for patients with unresectable malignant disease with short life expectancy, and an inability to tolerate an operation. Laparoscopic or open gastrojejunostomy and choledochojejunostomy are still effective options for selected patients. A randomized trial comparing laparoscopic bypass surgery to endoscopic procedure would give more information on the best outcome for these patients.

GALLBLADDER

The first laparoscopic cholecystectomy was in the mid 1980's. Doctors Muhe, Perissat, Berci, Cuschieri, Dubois, and Mouret all contributed to the development of this operation, and the beginning of a new era of laparoscopic abdominal surgery[48,49]. This section will focus on the management of cholecystitis, choledocholithiasis and gallbladder cancer.

Laparoscopic cholecystectomy is the preferred care for cholecystitis, cholelithiasis and biliary colic. It is safe and effective in elective and emergency setting even in the elderly[50]. Recent Cochrane reviews found that there is no significant difference between early and late laparoscopic cholecystectomy, for acute cholecystitis, in rate of bile duct injury, conversion rate, and operative time. However, the total hospital stay is shorter in the early group than the delayed group by four days. They also found that a laparoscopic cholecystectomy completed 24 h after diagnosis of biliary colic also decreased the morbidity, hospital stay and operating time during the waiting period of 4.2 mo[51,52]. With regards to the management of choledocholithiasis, whether the stones are managed intraoperative setting or with endoscopic retrograde cholangiopancreatography (ERCP), there is no difference with the patient's final outcome[53]. In addition, primary closure after laparoscopic common bile duct exploration

reduced hospital stay compared to T-tube drainage[54]. Post cholecystectomy complications, such as a bile leak, is now frequently managed with ERCP first[55]. Whether the cholecystectomy is completed *via* single-incision (SILC) or multiple-incisions (MILC), the long-term outcomes are the same. Recently reviewed by a Taiwanese group, they demonstrate that the SILC group had a faster recovery and shorter hospital stay than the MILC group by about one day[56]. The patients with more challenging gallbladder disease had longer operative times, longer hospital stays and higher conversion rates as compared to the uncomplicated group. Although the SILC group has a better cosmetic outcome, there is a higher hernia rate[57]. Patients with uncomplicated cholecystitis and choledocholithiasis benefit from laparoscopic cholecystectomy and common bile duct exploration when compared to an open operation. It is the complexity of the gallbladder pathology, which has more of an affect on operative time and hospital stay.

LIVER

In general, surgical resection is preferred to ablative procedures in the treatment of primary and secondary hepatic malignancy[58,59]. The guiding principles of hepatic resection are the need to leave the patient with at least 30% of functional hepatic reserve and at least 1 cm of tumor-free resection margin for malignant tumors[60,61]. Since its introduction by Gagner *et al*[17] in the early 1990s, hepatobiliary and liver transplant surgeons have increasingly adopted laparoscopic liver resection. An international survey completed by a Japanese group revealed that 88% of the participating centers have now adopted the laparoscopic liver resection[62]. The majority of these centers (76%) limited their indications to left lateral segmentectomy or limited resection of the peripheral parts of the liver. The other quarter of the institutions had applied laparoscopic approach to major hepatectomies or resection of tumors in the posterior part of the liver. Some institutions have also considered the laparoscopic approach to be feasible for donor hepatectomy[62]. As supported by numerous publications, this is a feasible and safe option for well-selected cases[62-64].

When planning a laparoscopic liver resection, lesion size, location, indication and surgical competency are all important. A Chinese study shows that laparoscopic liver resection is safe and feasible in patients with HCC with a tumor size of 5-10 cm[65]. This group also shows that as seen by previous groups, the length of stay is shorter, and the estimated blood loss is similar, and there is a lower post op complication such as wound infection[64,66,67]). In the past, laparoscopically accessible hepatic segments were in the peripheral segments of the liver (segments Ⅱ, Ⅲ, Ⅳb, Ⅴ, Ⅵ). The lesions in the non-laparoscopic segments were high and deep segments in the right side of the liver (segments Ⅵ, Ⅶ and Ⅷ)[62,68]. Many groups now report, that all segments of the liver can be approached with laparoscopic techniques[68,69]. As in any laparoscopic operation, the extraction wound is taken into consideration when planning the most efficient operation. Although better cosmetic results can be achieved with total laparoscopic method, this may not be feasible each time. Hand-assisted laparoscopic and laparoscopic assisted method are used by surgeons for unique resection such as with cirrhotic livers, laparoscopic resection of tumors in poor locations and living donor hepatectomies[70]. This study noticed that patients with hand-assisted laparoscopic liver resections had better perioperative outcomes.

Laparoscopic liver resection is safe and appropriate in the management of benign and malignant disease. Parks *et al*[68], 2013 completed a meta-analysis of long-term outcome comparing laparoscopic to open liver resections for the management of HCC and CRM in 1002 patients. They conclude there is no difference in survival up to a year. A systematic review by Rao *et al*[64] also demonstrate that laparoscopic liver resection has reduced overall complications, fewer positive margins and less blood transfusion requirements. Intraoperative low blood loss and hemostasis can be successfully achieved with the use of a Pringle maneuver, identification of anatomy, and appropriate use of energy devices, staplers, topical hemostatic agents and pressure[69]. In addition, Cheung *et al*[67] demonstrate that not only do patients with laparoscopic liver resections for HCC and CRM have a shorter hospital stay and less blood loss, the operative times are not that much longer, and the patients have a longer disease free survival. This would facilitate future reoperations for recurrent disease[66]. In the management of colorectal cancer, synchronous colorectal and liver resection has also been demonstrated to be feasible and safe as well[71].

The management of carcinoid liver metastasis is multimodal. The management of liver metastasis includes medical, radiological and surgical modes. Kandil *et al*[72] completed a retrospective analysis on 36 patients who had laparoscopic or open resections. The groups were similar in body mass index, tumor size, and incidence of carcinoid syndrome and extent of resection. Interestingly, the laparoscopic time was half that of open procedure time. There is less mean blood loss and shorter hospital stay. In addition, the three-year disease free survival of the laparoscopic group compared to the open group was better (73.3% *vs* 47.8%). These results support that laparoscopic liver resection is the preferred choice in the management of carcinoid liver metastasis[72].

Hepatic cysts are treated nonoperatively, interventional radiology or with surgery. The management of symptomatic hepatic cysts is almost routinely excised or marsupialized laparoscopically. Bacterial infected cysts are usually treated non-operatively and can be drained percutaneously. Hydatid cysts traditionally have been treated medically and excised. The possibility of rupturing a hydatid cyst and disseminating ecchinococcus makes percutaneous drainage and laparoscopic resection of these cysts less attractive. However, with multimodal therapy and at specialized centers, laparoscopic resection of hydatid cyst has been successful[73,74].

Overall, laparoscopic liver resection is feasible and has decreased blood loss and possibly better long term disease free survival when compared to an open operation, and when done by a surgeon skilled in hepatic laparoscopic surgery, in a supportive hospital.

CONCLUSION

Laparoscopic hepatobiliary and pancreas surgery for benign and malignant disease is just as safe and efficacious as open surgery. The benefit of this over open surgery includes smaller incisions, decreased wound infections, decreased blood loss and shorter hospital stay, as the result of a faster recovery rate. The increase in operative time in minimally invasive surgery may be due to the fact that there is a learning curve with each procedure. The use of hand assisted surgery or robotic surgery are useful in the extraction of large specimens and complex operations requiring the creation of multiple anastomoses. Minimally invasive surgery is safe and will be the preferred choice in the management of benign and malignant hepatobiliary and pancreatic disease in the future.

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MINIREVIEWS

Preoperative biliary drainage in hilar cholangiocarcinoma: When and how?

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Abstract

Hilar cholangiocarcinoma is a tumor of the extrahepatic bile duct involving the left main hepatic duct, the right main hepatic duct, or their confluence. Biliary drainage in hilar cholangiocarcinoma is sometimes clinically challenging because of complexities associated with the level of biliary obstruction. This may result in some adverse events, especially acute cholangitis. Hence the decision on the indication and methods of biliary drainage in patients with hilar cholangiocarcinoma should be carefully evaluated. This review focuses on the optimal method and duration of preoperative biliary drainage (PBD) in resectable hilar cholangiocarcinoma. Under certain special indications such as right lobectomy for Bismuth type ⅢA or Ⅳ hilar cholangiocarcinoma, or preoperative portal vein embolization with chemoradiation therapy, PBD should be strongly recommended. Generally, selective biliary drainage is enough before surgery, however, in the cases of development of cholangitis after unilateral drainage or slow resolving hyperbilirubinemia, total biliary drainage may be considered. Although the optimal preoperative bilirubin level is still a matter of debate, the shortest possible duration of PBD is recommended. Endoscopic nasobiliary drainage seems to be the most appropriate method of PBD in terms of minimizing the risks of tract seeding and inflammatory reactions.

Key words: Klatskin's tumor; Management; Jaundice; Endoscopic biliary drainage; Percutaneous biliary drainage; Preoperative biliary drainage

Core tip: In selected patients, optimal preoperative management will improve the morbidity and mortality of hilar cholangiocarcinoma. Endoscopic nasobiliary drainage seems to be the most appropriate method of preoperative biliary drainage (PBD) in terms of minimizing the risk of tract seeding and inflammatory reactions. Percutaneous transhepatic biliary drainage could be a better option in certain cases such as advanced hilar cholangiocarcinoma or segmental cholangitis. Total biliary drainage is not usually recommended except in certain situations when the surgical technique is difficult without PBD or when patients develop cholangitis after unilateral drainage or a slow-resolving hyperbilirubinemia. Although the optimal preoperative bilirubin level is still a matter of debate, the shortest possible duration of PBD is recommended.

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INTRODUCTION

Hilar cholangiocarcinoma (also known as a Klatskin tu-

mor) is an adenocarcinoma of the extrahepatic bile duct involving the left main hepatic duct, the right main hepatic duct, or their confluence[1]. Hilar cholangiocarcinoma has an extremely poor prognosis with a 5-year survival rate of less than 10%[2,3], and it is one of the most common causes of malignant biliary obstruction in the Asia-Pacific region[4]. Surgical resection is the only potentially curative treatment for hilar cholangiocarcinoma. Bile duct resection in combination with major hepatectomy is the standard treatment for hilar cholangiocarcinoma. This treatment modality achieves a higher cure rate compared to that with bile duct resection alone[5]. The morbidity and mortality of liver resection are significantly higher in patients with obstructive jaundice than in patients with normal liver function[6]. Therefore, preoperative biliary drainage (PBD) has been widely performed to reverse cholestasis-associated liver dysfunction and impaired hepatic regeneration[7,8]. The studies that analyzed PBD in hilar cholangiocarcinoma patients undergoing surgical resection are described in Table 1[8-15]. There are still controversies regarding the necessity of routine PBD since it can be associated with an increase in procedure-related adverse events[4]. A recently published meta-analysis on PBD in hilar cholangiocarcinoma revealed no clinical benefit and there were significant increases in postoperative adverse events, mainly infectious complications[16], which represent the most common complications after PBD[9,12]. Another recent multicenter retrospective study showed that PBD did not decrease postoperative morbidity and mortality in hilar cholangiocarcinoma[8]. However, in a subgroup analysis, PBD was noted to significantly decrease postoperative mortality in patients undergoing right hepatectomy by reducing postoperative liver failure. On the contrary, PBD tends to increase sepsis after surgery in patients undergoing left hepatectomy.

PBD may have some additional benefits in selected patients with severe malnutrition or biliary sepsis and in those undergoing delayed surgery due to portal vein embolization or chemoradiation therapy[17]. In addition, PBD may be indicated in patients with severe pruritus or renal failure[4]. Selective biliary drainage of preoperative intrahepatic segmental cholangitis plays an important role in reducing complications after major hepatic resection[18]. Moreover, cholangiography obtained by percutaneous transhepatic biliary drainage (PTBD) or endoscopic nasobiliary drainage (ENBD) can provide more precise information regarding the complicated segmental anatomy of the intrahepatic bile ducts and the extent of cancer along the separated ducts.

To date, the optimal serum bilirubin level for surgery is yet to be determined. Additionally, the optimal duration of PBD has not been clearly determined. Prolonged duration of biliary drainage would increase the risk of drainage malfunction, tract seeding, and secondary inflammatory changes to the bile duct. However, incomplete biliary drainage may increase the perioperative risks of liver resection[6]. Although biliary drainage differs between proximal and distal biliary obstructions, most studies analyzed the various levels of biliary obstruction as a single entity[19]. The patients heterogeneously showed a variety of serum bilirubin ranges and underwent different types of surgery. Despite the limitations, we focused on the optimal method and duration of PBD in resectable hilar cholangiocarcinoma. We searched electronic databases with the following keywords: "hilar cholangiocarcinoma", "Klatskin tumor", and "biliary drainage". The studies about preoperative biliary drainage in hilar cholangiocarcinoma from 1999 were reviewed and listed in this study.

OPTIMAL PREOPERATIVE DRAINAGE METHOD

In general, three methods in PBD are used in hilar cholangiocarcinoma: PTBD, endoscopic retrograde biliary drainage (ERBD) and ENBD. Yet, no randomized controlled trial has compared PTBD, ERBD and ENBD to identify the optimal method for PBD in hilar cholangiocarcinoma. ERBD has some advantages as it is more physiologic, improves nutritional status, reduces endotoxemia, normalizes dyslipidemia, and improves immune functions[19]. The endoscopic biliary drainage of hilar cholangiocarcinoma is often more challenging and complex. ERBD has the drawback of complicating the intraoperative evaluation of the longitudinal tumor extension and delaying the surgery[12,15]. The procedure-related morbidity and mortality rates of ERBD in proximal bile duct obstructions were 25%-50% and 3%-5%, respectively[12,20].

The procedure-related morbidity rates for percutaneous drainage were reported to be lower than those of endoscopic drainage[12]. PTBD was preferred to ERBD because of the reduction in both post-procedural cholangitis and the number of procedure sessions[12]. In particular, the success of biliary decompression is significantly higher with percutaneous stent insertion than with ERBD in advanced hilar cholangiocarcinoma[21]. Cholangiography obtained *via* the PTBD tube is helpful in determining the tumor extent and classification (Bismuth) before surgery. However, PTBD is an invasive technique in which is the tube penetrates through the liver parenchyma. The tumor seeding risk of this procedure is reported to be 5%-20%[22,23]. Gerhards *et al*[23] suggested that preoperative radiotherapy in patients with a resectable proximal bile duct cancer who underwent PBD, might decrease the risk of tumor dissemination. Further studies are required on the prevention of tract seeding after PBD.

In a recently published retrospective study, ENBD in the future remnant liver was considered the most suitable method for initial PBD management as compared with ERBD and PTBD[14]. ERBD had more frequent complications and PTBD was associated with serious complications such as vascular injuries and cancer dissemination. The inflammatory reaction around the bile duct would be less severe in ENBD because unlikely ERBD, ENBD does not cause duodenobiliary reflux[24]. Furthermore, ENBD is preferred to PTBD because it has no risk of

Table 1 Studies which have analyzed preoperative biliary drainage in hilar cholangiocarcinoma patients undergoing surgical resection

Ref.	Total number of patients with PBD	PBD-associated morbidity	Serum bilirubin before surgery (mg/dL)	Duration of PBD (d)	Postoperative morbidity	Postoperative complications	Infectious complications	5-year survival rate
Hochwald *et al*[9], 1999[1]	42 (PTBD 23; ERBD 13; intraoperative 3; ENBD 1; PTBD and ERBD 1; ERBD and ENBD 1)	-	5.6 ± 0.9	-	90%	5%	52%	-
Figueras *et al*[10], 2000[1]	11 (PTBD 11)	-	11.0 ± 9.4	16 ± 10	100%	9%	18%	25%
Ferrero *et al*[11], 2009[1]	30 (PTBD 18; ERBD 7; ERBD and PTBD 3; intraoperative 2)	23%	3.1 (0.3-14.1)	27.5 (10-90)	70%	3%	11%	-
Kloek *et al*[12], 2010[1]	101 (PTBD 11; ERBD 90)	76%	PTBD 1.1 ± 0.8; ERBD 1.3 ± 1.2	PTBD 11 (3-21); ERBD 15 (4-29)	-	-	48%	-
Grandadam *et al*[13], 2010[1]	12 (PTBD 12)	25%	4.1 ± 2.5	32 ± 9	13%	0	-	42%
Kawakami *et al*[14], 2011[1]	128 (PTBD 48; ERBD 20; ENBD 60)	Total 40% (PTBD 31%; ERBD 65%; ENBD 38%)	10.5 (2.2-29.3)	11.4 (1-154)	13%	3%	-	-
Ratti *et al*[15], 2013[1]	55 (PTBD 51; ERBD 4)	18%	3.4 ± 1.5	24 (10-36)	46%	5%	7%	29%
Farges *et al*[8], 2013[1]	180 (PTBD 104; ERBD 63; PTBD and ERBD 13)	33%	2.8 (1.2-5.6)	32	68%	9%	-	-

[1]All reports were retrospective studies. Data are expressed as mean ± SD or median (range). PBD: Preoperative biliary drainage; PTBD: Percutaneous transhepatic biliary drainage; ERBD: Endoscopic retrograde biliary drainage; ENBD: Endoscopic nasobiliary drainage.

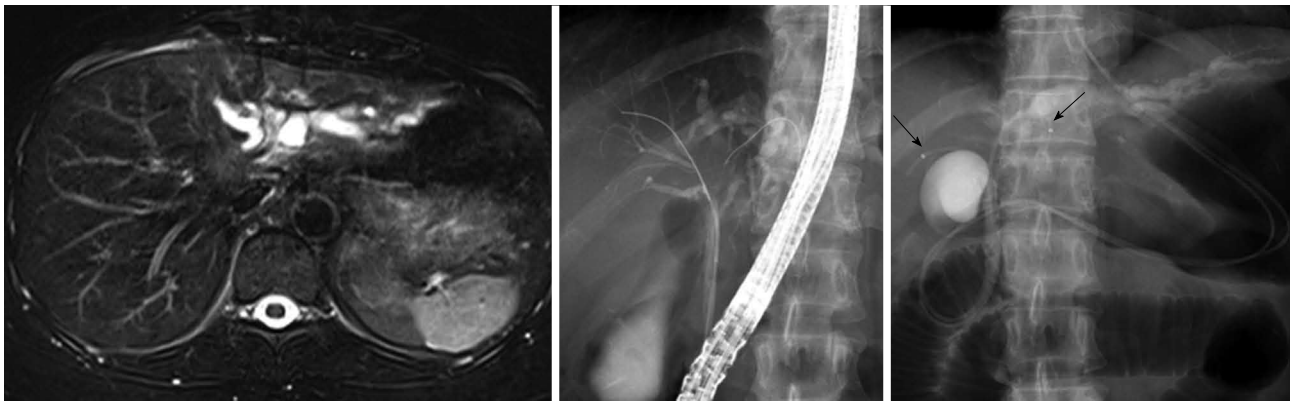

Figure 1 Forty-nine-year-old female with Bismuth type ⅢB hilar cholangiocarcinoma. Since contrast media were injected into both intrahepatic biliary ducts, bilateral endoscopic nasobiliary drainage was performed to prevent post-procedural cholangitis (Black arrows indicate the tip of nasobiliary tubes).

tumor spread along the drainage tract[14]. However, according to a recent report, ENBD was not effective in type Ⅳ hilar cholangiocarcinoma[25]. Patient discomfort and the risk of self-removal are other problems associated with ENBD. ENBD also often requires longer preoperative hospitalization[26]. The other disadvantage of ENBD is that it was previously impossible to drain both hepatic lobes[26]. At present, however, bilateral drainage with ENBD is technically feasible (Figure 1).

In summary, ERBD may not be a suitable option for initial PBD in hilar cholangiocarcinoma. ENBD seems to be preferred over PTBD as there is no risk of tract seeding and less invasiveness. The risk of tract seeding after PTBD has recently been reported to be lower than that reported in previous studies[27,28]. ENBD is less effective than PTBD in advanced hilar cholangiocarcinoma, in which there is a separation of the intrahepatic ducts. Therefore, we suggest that ENBD may be considered as the first line for initial PBD management in hilar cholangiocarcinoma. PTBD could be considered in some cases involving advanced hilar cholangiocarcinoma, segmental cholangitis, or delayed resolution of jaundice.

SELECTIVE VERSUS TOTAL BILIARY DRAINAGE: WHICH IS BETTER?

According to both experimental and clinical evidence, unilateral hepatic duct obstruction results in atrophy of the affected lobe and compensatory hypertrophy of the contralateral lobe[29]. Increased levels of hepatocyte growth factor due to biliary congestion might accelerate compensatory hypertrophy of the future remnant liver[30,31]. Furthermore, an experimental study proved that

Table 2 Recommended indication for preoperative biliary drainage and total biliary drainage in hilar cholangiocarcinoma

Preoperative biliary drainage	Right lobectomy for Bismuth type ⅢA or Ⅳ hilar cholangiocarcinoma
	Preoperative portal vein embolization and chemoradiation therapy
	Biliary infection of undrained bile duct
	Severe pruritus
Total biliary drainage	Development of cholangitis after selective drainage
	Slow resolution of hyperbilirubinemia
	Opacification of bilateral intrahepatic bile duct

the bile secretory capacity of the non-obstructed lobe is enhanced to compensate for the dysfunction of the obstructed lobes[32]. Preoperative selective biliary drainage will reduce bile stasis and induce hypertrophy with the enhancement of future remnant liver function[33,34]. The risk of segmental cholangitis might be a major weakness of selective biliary drainage[18]. Therefore, in cases where the surgical technique is difficult without PBD or when patients develop cholangitis after unilateral drainage or a slow resolving hyperbilirubinemia, total biliary drainage is preferred as it reduces the risk of cholangitis and preserves preoperative liver function[18,26,35,36]. Selectively applied and planned endoscopic drainage will reduce the use of contrast injections into atrophied and/or unintended multiple hepatic segments, which in turn reduces the incidence of post-procedural cholangitis[37-39].

The main limitation of previous studies comparing selective and total biliary drainage is selection bias. Since most of the studies were retrospective in nature, the choice between selective and total biliary drainage could be influenced by the degree of bile duct separation and the physician's preference. A randomized controlled study would be needed to minimize this selection bias.

OPTIMAL DURATION AND TARGET LEVEL OF PREOPERATIVE DRAINAGE

Although PBD is widely performed in hilar cholangiocarcinoma, its optimal duration has not been established. The latest Asia-Pacific consensus on recommendations for endoscopic and interventional management of hilar cholangiocarcinoma included recommendations for the optimal palliative management of hilar cholangiocarcinoma; however, there were no recommendations on optimal preoperative management[4]. In previous studies, the duration of PBD varied from 10 to 32 d[9,10,19,40-44]. After biliary drainage, the normalization of hyperbilirubinemia was achieved in only two-thirds of treated patients. It took approximately 4 to 8 wk to achieve a complete resolution of jaundice[26]. With respect to the duration of PBD, it was suggested that the adequate recovery of hepatic function depends on the duration of biliary decompression and the duration of obstructive jaundice before decompression[45,46]. However, the long-term maintenance of biliary drainage increases the risk of drainage malfunction[47,48]. Prolonged duration of PBD with ERBD causes an extensive inflammatory reaction within the bile duct[46,49,50]. It would cause bacterial translocation into the bile duct and the clogging of the stent, in addition to probably increasing the risk of post-operative leakage at the anastomosis site[46]. These drainage-related problems would result in a delay of surgery, which cannot be justified for a potentially resectable cancer[47]. Increased biliary drainage time was associated with a lower complete resection rate due to the possibility of tumor dissemination through the fistula tract[48]. A recent study revealed that PBD of more than 2 wk duration was not beneficial in reducing postoperative complications, whereas, drainage-related complications and hospital stay increased[48]. Therefore, a PBD duration of less than 2 wk would be more favorable in these jaundiced patients. Since most of the studies on the duration of PBD were retrospective in nature, the long duration of PBD might have caused the high rate of procedure-related adverse events and vice versa[48].

To restore the hepatic function of jaundiced patients, reducing the bilirubin level by decompression of the biliary obstruction is necessary. However, the optimal preoperative bilirubin level is still a matter of debate. A preoperative bilirubin level of less than 3 mg/dL was recommended by Makuuchi *et al*[33] and Nimura *et al*[36]. Su *et al*[51] reported that a preoperative bilirubin level of more than 10 mg/dL was significantly associated with postoperative mortality. Grandadam *et al*[13] reported that preoperative optimization of the liver in hilar cholangiocarcinoma reduced postoperative morbidity, and that the direct bilirubin level before surgery was 4.4 mg/dL. In a recent single center study, a total preoperative bilirubin level of more than 3 mg/dL was a negative factor affecting overall survival (HR = 2.109, 95%CI: 1.026-4.335)[52].

A longer period of PBD is required to achieve lower total bilirubin levels. However, to reduce procedure-related adverse events and to increase curative resections, surgery should not be delayed even if jaundice has not sufficiently resolved.

CONCLUSION

Optimal preoperative management for selected patients with hilar cholangiocarcinoma will improve morbidity and mortality. Under certain special indications such as right lobectomy for Bismuth type ⅢA or Ⅳ hilar cholangiocarcinoma, or preoperative portal vein embolization with chemoradiation therapy, PBD should be strongly recommended (Table 2). In most cases, selective PBD is adequate. Total biliary drainage is not usually recommended except in the development of cholangitis after unilateral drainage or slow resolving hyperbilirubinemia. Although the optimal preoperative bilirubin level is still a matter of debate, the shortest possible duration of PBD is recommended. ENBD seems to be the most appropriate method of PBD in terms of minimizing the risks of tract seeding and inflammatory reactions. PTBD could be a better option in certain cases such as advanced hilar cholangiocarcinoma or segmental cholangitis. A further

prospective randomized study comparing ENBD and PTBD is warranted.

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BRIEF ARTICLE

Factors predicting adverse short-term outcomes in patients with acute cholangitis undergoing ERCP: A single center experience

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Abstract

AIM: To identify potential factors that can predict adverse short-term outcomes in patients with acute cholangitis undergoing endoscopic retrograde cholangiopancreatography (ERCP).

METHODS: Retrospective analysis of consecutive patients admitted to our center for acute cholangitis and underwent ERCP from 2001 to 2012. Involvement of two or more organ systems was termed as organ failure (OF). Cardiovascular failure was defined based on a systolic blood pressure of < 90 mmHg despite fluid replacement and/or requiring vasopressor treatment; respiratory failure if the $Pa0_2/Fi0_2$ ratio was < 300 mmHg and/or required mechanical ventilation; coagulopathy if the platelet count was < 80; and renal insufficiency if serum creatinine was > 1.9 mg/dL. Variables associated with short term adverse clinical outcomes defined as persistent OF and/or 30-d mortality was determined.

RESULTS: A total of 172 patients (median age 62 years, 56.4% female) were included. The median door to ERCP time was 17 h. Bile duct stones were the most common etiology (n = 67, 39.2%). In multivariate analysis, factors that were independently associated with persistent OF and/or 30-d mortality included American Society of Anesthesiology (ASA) physical classification score > 3 (OR = 7.70; 95%CI: 2.73-24.40), presence of systemic inflammatory response syndrome (OR = 3.67; 95%CI: 1.34-10.3) and door to ERCP time greater than 72 h (OR = 3.36; 95%CI: 1.12-10.20). Door to ERCP time greater than 72 h was also associated with 70% increase in the mean length of stay (P < 0.001). Every one point increase in the ASA physical classification and every 1 mg/dL increase in the pre-ERCP bilirubin level was associated with a 34% and 2% increase in the mean length of hospital stay, respectively. Transfer status did not impact clinical outcomes.

CONCLUSION: Higher ASA physical classification and delays in ERCP are associated with adverse clinical outcomes and prolonged length of hospital stay in patients with acute cholangitis undergoing ERCP.

Key words: Endoscopic retrograde cholangiopancreatography; Cholangitis; Outcomes

Core tip: We investigated the effect of timing of endoscopic retrograde cholangiopancreatography (ERCP) on clinical outcomes defined as persistent organ failure and/or 30-d mortality, and length of hospital stay in

patients with acute cholangitis. We observed that an American Society of Anesthesiology physical classification score > 3, presence of systemic inflammatory response syndrome and door to ERCP time greater than 72 h are associated with adverse clinical outcomes and prolonged length of hospital stay in patients with acute cholangitis.

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INTRODUCTION

Bacterial cholangitis occurs in the setting of partial or complete biliary obstruction and is often secondary to bile duct stones. The bacteria gain access to the biliary tree by retrograde ascent from the duodenum (ascending cholangitis). Management of acute bacterial cholangitis requires antibiotics and/or relief of biliary obstruction[1-3]. This is usually accomplished by endoscopic retrograde cholangiopancreatography (ERCP)[1]. Bacterial cholangitis carries high mortality, approaching 10%, in the setting of sepsis with organ failure (OF)[1].

A number of studies have shown that endoscopic treatment of acute cholangitis is safe and effective[1-6]. However, our practices are guided by limited data and expert opinion. In author's experience emergent ERCP after appropriate resuscitation, in the form of antibiotics, intravenous fluids and stabilization of hemodynamic parameters is recommended. The Tokyo guidelines, based on expert opinion, recommend ERCP within 24 h of presentation in patients with acute cholangitis[7]. This recommendation was reinforced in a community-based study in which patients who underwent ERCP within 24 h of presentation had a shorter hospital stay[8]. In a prospective study of 95 patients with acute cholangitis, delay in biliary drainage was associated with increased risk of cholangitis complications and mortality[9]. A recently published study also suggests that failed or delayed (greater than 72 h) ERCP for acute cholangitis is associated with prolonged hospital stay, increased cost of hospitalization, and a worse composite clinical outcome (death, persistent organ failure, and/or intensive care unit stay)[10]. In addition to the timing of ERCP, presence of resistant organisms and elevated blood urea nitrogen has been associated with OF in patients undergoing ERCP[11]. Another study from our institution suggested that delays in ERCP may be associated with increased risk of 30-d readmissions[12]. Given the lack of strong evidence based data on the timing of ERCP on short term cholangitis outcomes and other predictors of OF, we sought to study the effect of timing of ERCP on clinical outcomes defined as persistent OF and/or 30-d mortality, and length of hospital stay (LOS) in patients with acute cholangitis.

MATERIALS AND METHODS

Patients

The Cleveland Clinic electronic medical records database was queried for patients admitted to our hospital and diagnosed with acute cholangitis who underwent ERCP from January 2001 to August 2012. After detailed review of medical records, patients without evidence of acute cholangitis were excluded. Demographic, clinical, and procedural data and adverse events were collected. The study was approved by the Cleveland Clinic Institutional Review Board.

Inclusion and exclusion criteria

The major inclusion criterion was presence of acute cholangitis as the indication for ERCP. Diagnosis of acute cholangitis was based on recorded signs and symptoms or documented purulent drainage from the bile duct during ERCP and/or positive blood cultures in patients with risk factors for acute cholangitis. Patients who were transferred from other hospitals to our endoscopy center just for the purpose of ERCP with return to the referring hospital immediately after the procedure were excluded. ERCP procedures were performed by one of eight experienced interventional endoscopists.

Collected variables

The medical records were reviewed for demographic, clinical, laboratory, and procedural information. The demographic and clinical variables, included age, gender, smoking status, alcohol use, body mass index, etiology of cholangitis, Charlson comorbidity index (CCI), presence of systemic inflammatory response syndrome (SIRS), ASA physical classification, presence of renal insufficiency (defined as defined as a serum creatinine > 1.9 mg/dL), use of anti-platelet agents (aspirin and/or clopidogrel), use of statins and LOS. Information was also obtained on whether the patient was transferred from outside hospitals or directly admitted to our hospital. The ASA physical classification at the time of the procedure was determined by the anesthesiologist and excluded the reason for ERCP (cholangitis).

Complete laboratory information including blood count, serum bilirubin and liver enzymes, coagulation panel and serum creatinine prior to ERCP, and results of blood cultures including possible isolated organism(s) were obtained.

Procedural information included success or failure of ERCP, door to ERCP time, presence of purulent discharge from the biliary orifice on endoscopy, and biliary sphincterotomy with or without stent placement during ERCP. Information on need for precut sphincterotomy, papillary balloon dilation, presence of biliary stricture, biliary stricture dilation, pancreatic duct injection and

post-ERCP adverse events were also collected.

All patients were started on intravenous antibiotics (with gram negative coverage) uniformly within 6 h of admission. In patients in whom cholangitis was not recognized at admission, broad spectrum antibiotics were started for fever of unknown origin within the time frame of 6 h.

Definitions

Failed ERCP was defined as unsuccessful cannulation of the bile duct. Door to ERCP time was defined as the time from admission to performance of ERCP. Pancreatic duct injection was defined as opacification of any portion of the pancreatic duct with contrast during the procedure. Post-ERCP complications were defined per ASGE workshop[13].

Involvement of two or more organ systems was termed as OF. The criteria were adapted from a previous study on definition of OF[10,14]. We included the involvement of the following organ systems for defining OF. Cardiovascular failure was defined based on a systolic blood pressure of < 90 mmHg despite fluid replacement and/or requiring vasopressor treatment; respiratory failure if the $Pa0_2/Fi0_2$ ratio was < 300 mmHg and/or required mechanical ventilation; coagulopathy if the platelet count was < 80; and renal insufficiency if serum creatinine was > 1.9 mg/dL. Persistent OF was recorded when OF was present for greater than 48 h. The 30-d mortality data was calculated using the Social Security Death Index to confirm the date of death, in addition to in hospital records for those who died while in the hospital.

Outcome measurement

The primary study aim was to identify potential variables associated with adverse clinical outcomes defined as persistent OF and/or 30-d mortality. The secondary aim was to investigate factors associated with prolonged LOS.

Statistical analysis

Descriptive statistics were computed for all factors. These include medians, 25% and 75%, range or mean and standard deviation for quantitative variables and frequencies and percentages for categorical factors. Continuous data are summarized as mean ± SD. Categorical data are summarized as frequency and group percentage. Normally distributed continuous variables were analyzed by using a *t* test, and continuous variables that were not normally distributed were analyzed by using the nonparametric (Wilcoxon) rank sum test. Logistic regression models were built for the primary outcome defined as persistent OF and/or mortality selecting from the various covariates associated with the end point at the 0.15 significance level and then choosing the best subset of covariates according to an overall model score test. The covariates in the model included age (forced covariate), gender, door to ERCP time (≤ 24, 24-48, 48-72 and > 72 h), CCI, ASA physical classification, anti-platelets, SIRS, biliary stent placement, total bilirubin levels, and presence of post-ERCP AEs. Logistic regression models were also built for prolonged LOS by backward selection by stepwise removal of variables at $P > 0.05$. The modeling of this outcome was most appropriate when performed on the Log_2 (LOS), since this transformed variable had far less skewness and much more symmetry in its distribution. R 2.10.1 software (The R Foundation for Statistical Computing, Vienna, Austria) was used to perform all analyses.

RESULTS

Query of the electronic medical records yielded 202 patients who were diagnosed with acute cholangitis who underwent ERCP. Thirty patients were excluded because of absence of confirmation of acute cholangitis after detailed review of the medical records. The remaining 172 patients were included in the analysis of outcomes. Table 1 highlights the characteristics of the entire cohort. Sixty-four (37.2%) patients were transferred from outside hospitals for further management of acute cholangitis; while the rest were directly admitted to our hospital. One hundred and eleven (64.5%) were admitted to the gastroenterology primary service, while the rest were admitted to other services (hepatobiliary, general surgery and other specialty services).

Univariate analyses

Univariate comparisons of continuous and categorical variables for patients with adverse clinical outcome (persistent OF or death) are shown in Table 2. Older age, CCI, higher ASA physical classification, presence of SIRS and fever were associated with worse clinical outcome. Anti-platelet agents and statin use at admission were not associated with adverse clinical outcome. Transfer status at admission did not impact the risk of adverse clinical outcome ($P = 0.41$). The presence of underlying PSC as the cause of cholangitis was associated with a decreased risk of adverse clinical outcomes, while post-liver transplant status was not associated with adverse clinical outcome.

Multivariate analyses

Factors that were independently associated with persistent OF and/or 30-d mortality included ASA physical classification > 3 (OR = 7.70; 95%CI: 2.73-24.40), presence of systemic inflammatory response syndrome (OR = 3.67; 95%CI: 1.34-10.3) and door to ERCP time greater than 72 h (OR = 3.36; 95%CI: 1.12-10.20) (Table 3). Of the 4 deaths, 2 occurred within the first 24 h and the other 2 deaths occurred with door to ERCP time of greater than 72 h. The two patients, who died within 24 h, succumbed in the intensive care unit with multi-organ failure and underwent ERCP on vasopressor support.

Reason for delay in ERCP

ERCP was delayed for 72 h in 29/172 (16.9%) patients. In 20/29 patients, comorbidity-associated factors such as

Table 1 Characteristics of study population and endoscopic retrograde cholangiopancreatography procedures *n* (%)

Variable	Value
Age (yr)	61.0 ± 16.9
Male	97 (56.4)
Race (white)	135 (80.8)
BMI (kg/m^2)	26.9 ± 5.9
Smokers	45 (37.5)
Alcohol consumption	19 (12.8)
With primary sclerosing cholangitis	48 (27.9)
With fever	105 (61.8)
With SIRS	33 (19.5)
Transfer patients	64 (37.4)
Patients admitted to gastroenterology service	111 (64.5)
Patients with post-liver transplantation	4 (2.3)
Charlson comorbidity index	
0	33 (19.4)
1	37 (21.8)
2	23 (13.5)
3	43 (25.3)
> 4	34 (20.0)
American Society of Anesthesiology Physical Classification	
1	2 (1.2)
2	2 (1.2)
3	101 (59.1)
4	62 (36.3)
5	4 (2.3)
Altered mental status	8 (4.7)
Medications at admission	
Antibiotics	126 (76.4)
Anti-platelets (aspirin and/or clopidogrel)	37 (22.3)
Statins	31 (18.7)
Etiology of cholangitis:	
Choledocholithiasis	67 (38.9)
Primary sclerosing cholangitis	45 (26.2)
Malignant stricture	28 (16.3)
Benign stricture	20 (11.6)
Others	12 (6.9)
Laboratory values:	
Pre-procedural bilirubin (mg/dL)	6.0 ± 5.0
Pre-procedural platelet count (cells/cu.mm)	189.4 ± 117.3
Pre-procedural international normalized ratio	1.2 ± 0.5
Serum creatinine during hospitalization (mg/dL)	1.3 ± 1.5
With positive blood culture	44 ± 31.7
Median time between admission and ERCP (h, range)	17 (1-240)
Who had ERCP within 24 h	104 (60.5)
Who had ERCP within 24-48 h	25 (14.5)
Who had ERCP within 48-72 h	14 (8.1)
Who has ERCP > 72 h	29 (16.9)
Purulent bile during ERCP	68 (40.5)
Dominant stricture during ERCP	32 (18.8)
Ampullary diverticulum	9 (5.3)
Balloon dilatation	69 (49.8)
Biliary sphincterotomy performed	50 (35.2)
Biliary stent placed	131 (77.1)
Pancreatic stent placed	14 (8.2)
Stone extraction	67 (39.2)
Failed ERCP	2 (1.2)
Complications post ERCP	
Bleeding	2 (1.2)
Pancreatitis	3 (1.8)
Perforation	2 (1.2)

Data are expressed as absolute numbers (percentage) or mean ± SD. SIRS: Systemic inflammatory response syndrome; ERCP: Endoscopic retrograde cholangiopancreatography; BMI: Body mass index.

Table 2 Univariate analysis for adverse clinical outcome in 35 patients

Variable	OR (95%CI)	*P* value
Age	1.15 (1.02-1.30)	0.02
Male	0.90 (0.43-1.89)	0.78
Body mass index	1.23 (0.88-1.71)	0.23
Smoking	0.62 (0.22-1.72)	0.36
Primary sclerosing cholangitis	0.27 (0.09-0.82)	0.02
Systemic inflammatory response syndrome	5.46 (2.34-12.73)	< 0.001
Charlson comorbidity index	1.02 (0.85-1.23)	0.04
American Society of Anesthesiology physical classification	6.94 (3.14-15.33)	< 0.001
Altered mental status	1.31 (0.25-6.80)	0.61
Statins at admission	2.32 (0.97-5.57)	0.06
Anti-platelets meds at admission	2.18 (0.93-5.07)	0.07
Door to ERCP timing (> 72 h)	2.03 (0.83-4.95)	0.12
Pre-ERCP Bilirubin	1.05 (0.98-1.12)	0.20
Positive blood cultures	1.79 (0.79-4.10)	0.17
Presence of fever	2.87 (1.17-7.04)	0.02
Post ERCP bleeding	4.00 (0.24-65.59)	0.37
Presence of purulent bile at ERCP	1.41 (0.45 -5.40)	0.73
Transfer patients	0.72 (0.32-1.59)	0.41

ERCP: Endoscopic retrograde cholangiopancreatography.

Table 3 Multivariate analysis for adverse clinical outcome in 35 patients

Variable	OR (95%CI)	*P* value
American Society of Anesthesiology physical classification > 3	7.70 (2.73-24.4)	< 0.001
Systemic inflammatory response syndrome	3.67 (1.34-10.3)	0.01
Age (per 5 years)	1.05 (0.89-1.26)	0.54
Door to ERCP time > 72 h	3.36 (1.12-10.2)	0.03
Primary sclerosing cholangitis	0.41 (0.09 -1.49)	0.20
Bile duct stent placement	0.70 (0.23-2.19)	0.52
Charlson comorbidity index	0.89 (0.69-1.13)	0.37

ERCP: Endoscopic retrograde cholangiopancreatography.

severe coagulopathy, hepatic encephalopathy or decompensated congestive heart failure precluded immediate ERCP. These patients required resuscitation prior to performance of any invasive procedure. In seven patients, cholangitis appeared to have been present for several days before it was recognized. Two other patients had metastatic cancer to the bile duct (primary breast and renal cell carcinoma). These patients had presented with fever of unknown origin and cholangitis was recognized only after 48 h. All these patients were on broad spectrum antibiotics started within 6 h of admission. There was no impact of service or day of admission on clinical outcomes of patients.

Length of stay

In unadjusted analysis, increasing door to ERCP time was directly associated with an increase in LOS (Table 4, Figure 1A). Patients who underwent ERCP after 72 h were more than three and half times more likely to have a LOS beyond 10 d as compared to those who underwent an ERCP within 24 h of admission. Higher ASA physical classification and presence of persistent cardiovas-

Table 4 Univariate analysis for length of stay of greater than 10 d (90th percentile)

Variable	OR (95%CI)	*P* value
Age	1.05 (0.92-1.19)	0.47
Male	0.98 (0.42-2.31)	0.97
Body mass index	1.07 (0.71-1.60)	0.74
Smoking	1.13 (0.37-3.41)	0.83
Primary sclerosing cholangitis	0.60 (0.21-1.71)	0.34
Systemic inflammatory response syndrome	2.02 (0.75-5.40)	0.16
Charlson comorbidity index	1.04 (0.85-1.28)	0.69
American Society of Anesthesiology physical classification > 3	3.12 (1.47-6.63)	0.003
Altered mental status	2.03 (0.39-10.67)	0.33
Statins at admission	0.90 (0.28-2.88)	1
Anti-platelets meds at admission	1.03 (0.35-3.01)	1
Door to ERCP time		
≤ 24 h (reference)	-	-
24-48 h	2.66 (1.12-6.34)	0.03
48-72 h	2.82 (1.17-6.82)	0.02
> 72 h	3.57 (1.39-9.17)	0.03
Pre-ERCP bilirubin	1.07 (0.99-1.15)	0.08
Positive blood cultures	1.70 (0.69-4.21)	0.25
Presence of fever	1.04 (0.43-2.53)	0.94
Post-ERCP pancreatitis	3.00 (0.26-34.39)	0.38
Serum creatinine at admission	1.48 (1.13-1.94)	0.004
Presence of persistent cardiovascular failure	3.18 (1.15-8.79)	0.04
Presence of persistent respiratory failure	13.81 (2.38-80.11)	0.004
Presence of persistent renal failure	4.81 (1.74-13.29)	0.004
Transfer patients	0.93 (0.39-2.25)	0.87

ERCP: Endoscopic retrograde cholangiopancreatography.

cular, renal and respiratory failure were associated with prolonged LOS beyond 10 d. The transfer status of the patient was not associated with prolonged LOS (Table 4). On multi-variate analysis, door to ERCP time greater than 72 h was associated with 70% increase in the mean LOS. Every 1 point increase in the ASA physical classification score, and every 1 mg/dL increase in pre-ERCP serum bilirubin levels was associated with a 34% and 2% increase in the mean LOS respectively (Figure 1B). Patients who developed post-ERCP adverse events had a 91% increase in the mean LOS (Table 5).

DISCUSSION

Although the safety and efficacy of endoscopic treatment in patients with acute cholangitis has been demonstrated in a number of studies[1-7], the literature on timing of endoscopy and its impact on cholangitis outcomes remains limited. In our study, delayed ERCP was associated with adverse clinical outcomes including persistent OF and/or 30-d mortality. Despite adjustments for disease severity, there was a significant association between door to ERCP time and LOS. It is also important to realize that the presence of co-morbidities contributed to this delay in ERCP.

In a previously published study of 90 patients, older age, increased serum bilirubin levels and ERCP delay of 72 h were associated with adverse clinical outcomes of intensive care unit (ICU) stay, persistent OF, and death[10]

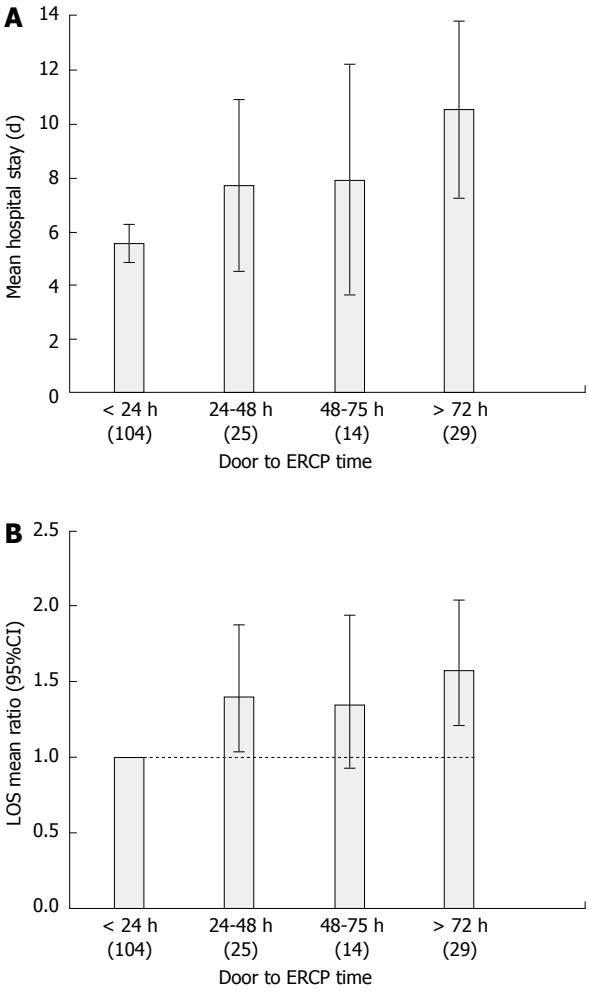

Figure 1 Comparison of the unadjusted (A) and adjusted (B) mean length of stay in patients based on door to endoscopic retrograde cholangiopancreatography time. A: Patients had a progressive increase in the mean length of stay based on a 24 h increase in the door to endoscopic retrograde cholangiopancreatography (ERCP) time; B: Patients with a door to ERCP time greater than 72 h had a significant increase in mean length of stay.

In our study, after adjustments for ASA physical classification and CCI, neither age nor serum bilirubin levels were predictors of adverse outcomes. This discrepancy is likely due to different study designs and statistical analyses. The previous study did not make adjustments for variables such as ASA physical classification, and transfer status of the admitted patients which could potentially impact clinical outcomes[10]. In addition, the sample size was limited to study the defined variables, Furthermore, the decision to include ICU admissions in the composite outcome may be biased as ICU admissions may have different thresholds in different hospitals. To avoid this selection bias, we did not include ICU stay in our definition of clinical outcomes. It should also be pointed out that the associated conditions that led to delays in ERCP, such as hemodynamic instability or unrecognized cholangitis, may be contributing to worse outcomes and prolonged LOS in these patients.

The number of SIRS criteria has in previous studies been associated with the risk of death from sepsis of

Table 5 Multivariate analysis for mean length of stay

Variable	OR (95%CI)	*P* value
American Society of Anesthesiology physical classification (every 1 class)	1.34 (1.19-1.52)	< 0.001
Door to ERCP time		
≤ 24 h (reference)	-	-
24-48 h	1.22 (0.97-1.54)	0.09
48-72 h	1.24 (0.92-1.66)	0.16
> 72 h	1.70 (1.36-2.12)	< 0.001
Pre-ERCP bilirubin (every 1 mg/dL)	1.02 (1.01-1.04)	0.02
Post-ERCP bleeding or pancreatitis	1.91 (1.12-3.24)	0.02
Charlson comorbidity index	1.01 (0.96-1.06)	0.74
Positive blood culture	1.18 (0.96-1.46)	0.12

Modeling of this outcome performed on the Log2 (length of stay), since this transformed variable had less skewness and much more symmetry in its distribution. ERCP: Endoscopic retrograde cholangiopancreatography.

various etiologies[15,16]. Our study results are in line with those of prior studies in which SIRS criteria have been used to predict outcomes in acute cholangitis[17,18]. In a large study from Hong Kong, a heart rate above 100/min was associated with requirement for emergent ERCP[16]. Similar findings were reported in a French study[18].

Previous studies have suggested that older age is a risk factor associated with significant mortality in acute cholangitis[19-21]. In our study, older age was associated with adverse outcomes only on univariate analysis. However, on multivariate analysis when adjustments were made for co-morbidities including the ASA physical classification, age lost its significance. We believe that this discrepancy is mainly because in prior studies comorbidities were not taken into consideration.

In our study, higher ASA physical classification was associated with adverse short term outcomes and increase in LOS in patients with acute cholangitis. Previous studies have shown correlation of ASA physical classification with hospital LOS, postoperative infections, and overall morbidity and mortality rates following surgical procedures[22,23]. Higher ASA physical classifications were also shown to correlate with a higher incidence of cardiopulmonary events in a large study of the Clinical Outcomes Research Initiative database[24]. Thus the ASA physical classification may be an important prognostic indictor in patients with acute cholangitis. As expected, most of the patients in our cohort were ASA physical classification 3 or 4 reflecting the nature of most tertiary center practices.

It was not surprising that patients with renal insufficiency and those who developed persistent OF and post-ERCP AEs had a longer duration of hospital stay. It is possible that the same factors that increase the risk of AEs may also influence prolonged hospital stay. It may also reflect a delayed general recovery after developing an AE in patients with underlying comorbidities who undergo emergent ERCP for acute cholangitis. In a large study published in the abstract form, elevated blood urea nitrogen was identified as an important predictor of mortality[11]. In our patient cohort, higher pre-ERCP bilirubin was also associated with prolonged hospital stay. In a recent study, elevated bilirubin was identified as a predictor of worse outcomes and OF[10]. Bilirubin at high concentrations has been shown to induce inflammation, apoptosis, and oxidative stress[25,26]. In a large study, higher bilirubin at admission was associated with subsequent development of sepsis-related acute respiratory distress syndrome and death[27].

Some studies in acute pancreatitis have shown worse outcomes in patients transferred from other hospitals compared to those admitted directly[28,29]. The proposed reason is that transfer patients are sicker resulting in worse outcomes. We did not observe any association between transfer status and clinical outcomes in acute cholangitis. In our cohort only 7/64 transferred patients had a door to ERCP time of greater than 72 h. Based on their CCI and ASA physical classification, transferred patients were not sicker than those directly admitted to our hospital and had a similar incidence of OF during their hospitalization and similar LOS.

The large sample size, statistical adjustments for multiple clinical covariates, and the uniformity of practice patterns for the treatment of cholangitis in a single tertiary care institution are the strengths of this study. Our study has several limitations. First, this is a retrospective study with all inherent limitations of a retrospective design. Second, we studied the association of door to ERCP time with clinical outcomes. Since some patients may have had symptoms for several days before clinical presentation, the time from symptom development to ERCP may be a better factor to study than door to ERCP time. We could not obtain information on symptom to ERCP time because of retrospective nature of the study. However, despite these limitations, our study presents compelling evidence that door to ERCP time and co-morbidities are important predictive factors for adverse outcomes in patients with acute cholangitis.

To conclude, delay in performing ERCP and comorbidities are associated with adverse clinical outcomes and prolonged LOS in patients with acute cholangitis. Future strategies to address these issues and to improve outcomes in patients with acute cholangitis need evaluation.

COMMENTS

Background

Predictors of adverse short-term outcomes in patients with acute cholangitis are unclear. There is lack of strong evidence based data on the timing of endoscopic retrograde cholangiopancreatography (ERCP) on short term cholangitis outcomes and other predictors of organ failure.

Research frontiers

A recently published study suggests that failed or delayed (greater than 72 h) ERCP for acute cholangitis is associated with prolonged hospital stay, increased cost of hospitalization, and a worse composite clinical outcome (death, persistent organ failure, and/or intensive care unit stay). There is lack of strong evidence based data on the timing of ERCP on short term cholangitis outcomes. In this study, the authors have demonstrated that higher American Society of Anesthesiology (ASA) physical classification and delays in ERCP are associated with adverse clinical outcomes and prolonged length of hospital stay.

Innovations and breakthroughs

Although a previous study demonstrated that ERCP delay of 72 h was associated with adverse clinical outcomes of intensive care unit (ICU) stay, persistent organ failure (OF), and death, adjustments for variables such as ASA physical classification, and transfer status of the admitted patients which could potentially impact clinical outcomes was not done. This study has clearly demonstrated that higher ASA physical classification and delays in ERCP are associated with adverse clinical outcomes and prolonged length of hospital stay.

Applications

By understanding how delay in ERCP impacts outcomes, this study may represent a future strategy for improving timing of therapeutic intervention in the treatment of patients with acute cholangitis.

Terminology

Involvement of two or more organ systems was termed as OF. Door to ERCP time was defined as the time from admission to performance of ERCP.

Peer review

This paper reports a carefully performed retrospective single center study analyzing factors predicting adverse short-term outcomes in patients with acute cholangitis undergoing ERCP. According to the dataset which is based upon 172 patients, higher ASA physical classification and delay in ERCP are both associated with adverse clinical outcome and prolonged length of hospital stay in patients with acute cholangitis. Overall this is a well written and clinically important study.

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BRIEF ARTICLE

Feasibility of breath monitoring in patients undergoing elective colonoscopy under propofol sedation: A single-center pilot study

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Abstract

AIM: To determine whether a newly developed respiratory rate monitor can practically and accurately monitor ventilation under propofol sedation in combination with standard monitoring.

METHODS: Patients [American Society of Anesthesiologists (ASA) Classification Ⅰ-Ⅲ] scheduled for elective colonoscopy under propofol sedation were monitored with a new device that measures the respiratory rate based on humidity in expired air. Patients with clinically significant cardiac disorders or pulmonary disease and patients requiring emergency procedures were excluded from study participation. All of the patients also received standard monitoring with pulse oximetry. This was a single-center study conducted in a community hospital in Switzerland. After obtaining written informed consent from all subjects, 76 patients (51 females and 25 males) were monitored during colonoscopy under propofol sedation. The primary endpoint was the occurrence of any respiratory event (apnea or hypopnea). Apnea was defined as the cessation of breathing for a minimum of 10 s. Significant apnea was defined as the cessation of breathing for more than 30 s. Hypopnea was defined as a reduction in the respiratory rate below 6/min for a minimum of 10 s. Any cases of significant apnea triggered interventions by the endoscopy team. The interventions included withholding propofol, verbal stimulation of the patients, and increased oxygen supplementation or the chin lift maneuver. A secondary endpoint was the correlation of apnea or hypopnea with hypoxemia (measured as a decrease in SaO_2 of at least 5% from baseline or less than 90%).

RESULTS: At least one respiratory event was detected in thirty-seven patients (48.7%). In total, there were 73 respiratory events, ranging from one to six events in a single patient. Significant apnea (> 30 s) occurred in five patients (6%). Only one episode of apnea led to a relative SaO_2 reduction (from 98% to 93%) after a 50 s lag time. No event requiring assisted ventilation was recorded. Our analysis revealed that the total propofol dose was an independent risk factor for respiratory events (P = 0.01). Artifacts developed with the same frequency with the new device as with conventional pulse oximetry. Compared with pulse oximetry alone, this new monitoring device detected more respiratory events and may provide earlier warning of impending respiratory abnormalities.

CONCLUSION: Apnea commonly occurs during endoscopy under sedation and may precede hypoxemia. We recommend this respiration rate monitor as an alternative to capnography to aid in detecting ventilatory problems.

Key words: Apnea; Colonoscopy; Conscious sedation; Deep sedation; Propofol; Pulse oximetry; Respiratory monitoring

Core tip: Apnea monitoring is a useful adjunct in assessing the ventilatory status of patients undergoing sedation. Capnography is too expensive to be used dur-

ing normal endoscopic procedures. A newly developed respiratory rate-monitoring device based on the humidity of expired air enables the real-time assessment of ventilation. Compared with pulse oximetry alone, this new monitoring device detected more respiratory events and may provide earlier warning of impending respiratory abnormalities.

Anand GW, Heuss LT. Feasibility of breath monitoring in patients undergoing elective colonoscopy under propofol sedation: A single-center pilot study. *World J Gastrointest Endosc* 2014; 6(3): 82-87 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i3/82.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i3.82

INTRODUCTION

Colonoscopy is established as a routine intervention to diagnose and treat colonic diseases. It is recommended as the most efficient screening procedure to detect colon cancer[1,2]. The acceptance and tolerance of the procedure has remarkably increased with the use of a sedative agent[3,4]. The short-acting sedative propofol is an ideal drug with a superior pharmacokinetic profile: an excellent amnestic effect, a rapid onset of action, and a short half-life of 4 min[5-7]. In many European countries (*e.g.*, Switzerland), propofol is administered under the guidance of a gastroenterologist without the assistance of an anesthesiologist in most routine endoscopic procedures[8-11].

Propofol is administered as a bolus at repeated intervals to achieve a level of moderate sedation in which the patient is still responsive to verbal or tactile stimulation[12]. Nevertheless, carefully sedated patients can potentially progress into deeper levels of sedation[10,13]. Drug-induced respiratory depression and airway obstruction are the leading causes of morbidity during sedation and are the most feared complications of propofol because there is no antidote[6,12]. Thus, standard patient monitoring includes pulse oximetry as a surrogate measure of ventilation[12,14]. Normal SaO_2 does not ensure adequate ventilation. Apnea and hypoventilation precede hypoxemia with a significant lag time of up to 2 min. In previous studies, capnography was shown to increase the detection of adverse respiratory events[15-17]. However, capnography is expensive, and its use relies on the observation of the breath curve.

In this study, we sought to determine whether breath monitoring with a newly developed respiratory rate-monitoring device based on the humidity of expired air could be a practical and accurate method of monitoring ventilation under sedation in addition to standard monitoring with pulse oximetry.

MATERIALS AND METHODS

Study population

This was a single-center pilot study to assess the practicability of breath monitoring with a newly developed respiratory rate-monitoring device (respiR8™) during propofol sedation in patients undergoing colonoscopy. The study protocol was reviewed and approved by a local ethics committee in Zurich, Switzerland.

All consecutive patients presenting for an inpatient or outpatient diagnostic colonoscopy in a community hospital endoscopy center (Zollikerberg Hospital, Zurich, Switzerland) were considered for enrollment if they met all of the following inclusion criteria: (1) age ≥ 18 years; (2) ASA class Ⅰ-Ⅲ; and (3) ability to provide informed consent.

Patients were excluded from enrollment if they met any of the following exclusion criteria: (1) ASA class Ⅳ or Ⅴ; (2) inability to give informed consent; (3) emergency procedure, (4) allergy to propofol; and (5) pregnant. After providing written informed consent, 76 patients (51 females and 25 males) were included in this study.

RespiR8™ (Anaxsys Technology Ltd., United Kingdom) is a European community-certified device specifically developed to allow continuous monitoring of the respiratory rate of patients requiring oxygen delivered by a face mask. Its use in the postoperative recovery setting has been tested successfully[18]. The device comprises a disposable oxygen mask fitted with Anaxsys' patented sensor, which measures moisture in the exhaled breath. The respiR8™ monitor displays the current respiratory rate and has a trend screen that shows the respiratory rate over time (Figure 1).

The respiR8™ humidity sensor consists of a ceramic substrate printed with two gold interdigitated electrodes that are coated with an ion exchange polymer. This polymer is a highly proton-conductive fluoropolymer. A small current is applied across the electrodes, and as the patient exhales, moisture condenses on the surface of the sensor. Due to the presence of the moisture, ions from the coating migrate between the electrodes and produce an electric signal (the greater the amount of moisture, the greater the signal). As the patient inhales, the surface of the sensor is dried by a flow of ambient air passing over the surface, and the signal returns to baseline. The analog signal is then converted to a digital signal. An algorithm in the monitor detects the peaks in the signal and converts the signal into a respiratory rate value.

Patient demographics and procedure variables

Each patient's age, gender, ASA status, and indication for colonoscopy were recorded. The ASA status and the indication for colonoscopy were determined by the endoscopist. The duration of colonoscopy was defined as the time from the introduction to the withdrawal of the endoscope. The total dose of propofol used during the procedure was considered a procedural variable.

Study procedure

Sedation: A gastroenterologist-directed sedation technique was applied to achieve and maintain an adequate level of sedation, as described elsewhere[14]. After an initial intravenous dose of 20 mg of propofol (Disoprivan

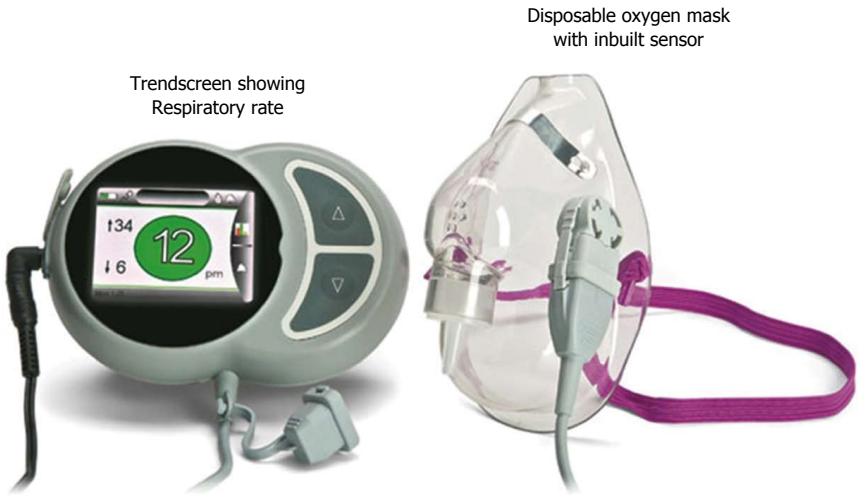

Figure 1 Respiratory rate-monitoring device is comprised of a monitor and an oxygen mask with a built-in sensor.

1%, AstraZeneca, London, GB), repeated doses of 10-20 mg of propofol were administered intravenously (with no limit on the total dose). All monitoring values were confirmed before administering doses of propofol. No other sedation medication was used during the procedure.

Monitoring: According to the standard operation procedures of our unit, all of the patients underwent continuous monitoring of their heart rate and SaO_2 with a pulse oximeter and BP measurement at 5-min intervals[14]. Additionally, all of the patients were continuously monitored with respiR8™ to record respiratory events. A disposable respiR8™ mask covering the patient's nose and mouth was attached to an oxygen supply, which provided continuous oxygen at a rate of 2 L/min.

The SaO_2 display and respiR8™ display were placed near the endoscopy monitor to facilitate continuous observation by the gastroenterologist and the endoscopy nurse. The data from the respiR8™ device and the pulse oximeter were saved directly in a personal computer using a USB connection. All of the recorded data were transferred into an individual patient file numbered according to the usual case numbering system in our hospital. The clocks on the endoscopy monitor, the SaO_2 device, and the respiR8™ device were all synchronized.

Approximately four minutes following completion of the colonoscopy, the patients were disconnected from the monitoring device when they could give meaningful verbal responses and their vital signs were stable.

All of the patients were monitored for several minutes before the first dose of propofol was administered, which signaled the beginning of sedation. Any sign of apnea or hypoxemia prompted a clinical observation of chest movement and patient stimulation to exclude artifacts in the respiR8™ or pulse oximeter and signs of mask displacement. Significant apnea permitted the use of a chin lift or jaw thrust maneuver, increasing the oxygen supplementation, and withholding further propofol doses where appropriate.

Study outcome

The primary study outcome was the occurrence of any respiratory event (apnea or hypopnea). Apnea was defined as the cessation of breathing for at least 10 s. Significant apnea was defined as the cessation of breathing for more than 30 s[19]. Hypopnea was defined as a reduction in the respiratory rate below 6/min for a minimum of 10 s. The secondary end point was the correlation of apnea or hypopnea with hypoxemia (defined as a decrease in SaO_2 of at least 5% from baseline or less than 90%)[15]. The time of sedation was defined from the start of the first administration of propofol until the disconnection of electronic monitoring devices after the procedure was complete.

Statistical analysis

Continuous variables and count data are presented as means with standard deviations or as medians with ranges. The data were compared between patients with and without respiratory events using the Mann-Whitney test with exact *P*-values. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test where appropriate. A two-tailed *P*-value of less than 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL).

RESULTS

From July 2011 to November 2011, 76 patients presenting for an elective diagnostic colonoscopy were enrolled in the study. The mean procedure duration was 17.2 ± 6.4 min. The demographic data are shown in Table 1.

Primary study outcome

In this study, 37 (48.7%) patients developed at least one respiratory event (Table 1). There were 73 respiratory events, ranging from one to a maximum of six events in a single patient. Significant apnea lasting for more than

Table 1 Demographic characteristics

	Event (n = 37)	No event (n = 39)	P value
Age (yr)	60.8 (± 18.6)	67.8 (± 18.9)	NS
Male:female (25:51)	12:25	13:26	NS
ASA Ⅰ (21)	12	9	NS
ASA Ⅱ (22)	12	10	NS
ASA Ⅲ (33)	13	20	NS

Data are shown as absolute numbers or means (± SD) as indicated; NS: Not significant.

Table 2 Correlation of the total propofol dose with respiratory events and SaO_2

	Event (n = 37)	No event(n = 39)	P value
Total propofol dose (mg)	228.6 (± 78.8)	189.5 (± 81.6)	0.01
SaO_2 mean (%)	99.86 (± 0.4)	99.73 (± 0.7)	NS

Data are given as the mean (± SD); NS: Not significant.

30 s occurred in five patients (6%).

Secondary study outcome

In one case, apnea led to a relative SaO_2 reduction within the physiologic range (from 98% to 93%) after a lag time of 50 s. There were no serious hypoxemia events in our study.

Relationship between respiratory events and total propofol dose

The mean propofol dose used in patients who had no respiratory events was 189.5 ± 81.6 mg compared with 228.7 ± 70.8 mg in patients who had respiratory events (P = 0.01). The mean SaO_2 values did not differ significantly in patients with or without respiratory events. Our analysis revealed that the total propofol dose was an independent risk factor for respiratory events (P = 0.01) (Table 2).

Artifacts affecting the results of the respiration counter occurred in 36.5% of patients without respiratory events and in 41.6% of patients with respiratory events. These artifacts were related to superficial breathing, incorrect positioning of the oxygen mask, coughing, snoring, or a chin drop. Superficial breathing could be verified by palpating the chest movement of the patient.

Graphic monitoring of SaO_2 and the respiratory rate is shown in Figure 2. Artifacts from the pulse oximetry device occurred in 36.9% of patients without respiratory events and in 41.2% of patients with respiratory events. SaO_2 artifacts were related to the dysfunction of the SaO_2 monitor or the displacement of the SaO_2 sensor on the patient's finger during repositioning. No event requiring assisted ventilation was recorded.

DISCUSSION

Our study is the first prospective evaluation of the continuous monitoring of breathing during propofol sedation in patients undergoing colonoscopy with a new respiratory rate-monitoring device. In 48.7% of our patients, the device detected at least one episode of a respiratory event defined as apnea or hypopnea. Notably, none of the events were detected by monitoring with pulse oximetry alone. This result correlates with previous studies demonstrating that abnormal respiratory events detected with capnography occurred in more than 50% of patients[6,15]. Although pulse oximetry is considered the de facto standard of care for the detection of respiratory depression during endoscopic procedures, our study confirms that it could be potentially misleading to rely only on pulse oximetry as a surrogate marker of alveolar hypoventilation[20-22]. As shown by Vargo *et al*[19], significant alveolar hypoventilation can occur during endoscopic procedures even in the presence of a normal level of SaO_2, as measured by pulse oximetry. Despite the identified episodes of hypoventilation in our study, the measured mean SaO_2 did not differ significantly. In one case, an apnea registered by the respiR8™ device led to a relative SaO_2 reduction of 5% within the physiologic range (from 98% to 93%) after a lag time of 50 s. Therefore, we assume that short episodes of apnea or hypoventilation occur at a higher rate than expected based on pulse oximetry monitoring.

Guidelines for propofol sedation by non-anesthesiologists recommend ventilation monitoring[12]. This monitoring can be accomplished by direct observation or the palpation of chest wall excursions[23]. However, these approaches may be impractical in darkened endoscopy rooms and require additional attention from the available personnel for visual or tactile assessment. Routine ventilation monitoring using an oxygen mask could facilitate patient observation and enable the assistant to perform tasks that are more demanding. Many gastroenterologists use capnography to monitor the respiratory rate and for the early detection of apnea. The respiR8™ device may be a suitable alternative for these physicians. Compared to capnography, the studied device is less expensive and easier to use because the focus is on the respiratory rate and not on the measured value of CO_2. The costs associated with the use of the respiR8™ device include the onetime cost of the device (approximately USD 940) and the cost of a disposable mask (approximately USD 10) that allows concurrent oxygen administration.

In this study, 73 respiratory events were detected, but no serious respiratory events requiring bag mask ventilation occurred. The patient sample size was likely too small to observe such an event, which occurs in only 0.1% of routine sedations[10]. Therefore, we speculate that respiratory events detected with the respiR8™ device may precede the development of reduced SaO_2 and could serve as an early warning system for impending respiratory compromise. Further studies are required to confirm the potential benefit of additional respiratory rate monitoring.

Consistent with previous findings, there was no difference among patients with or without respiratory events with respect to ASA classification, age, or indication of colonoscopy[14]. The total propofol dose used was an in-

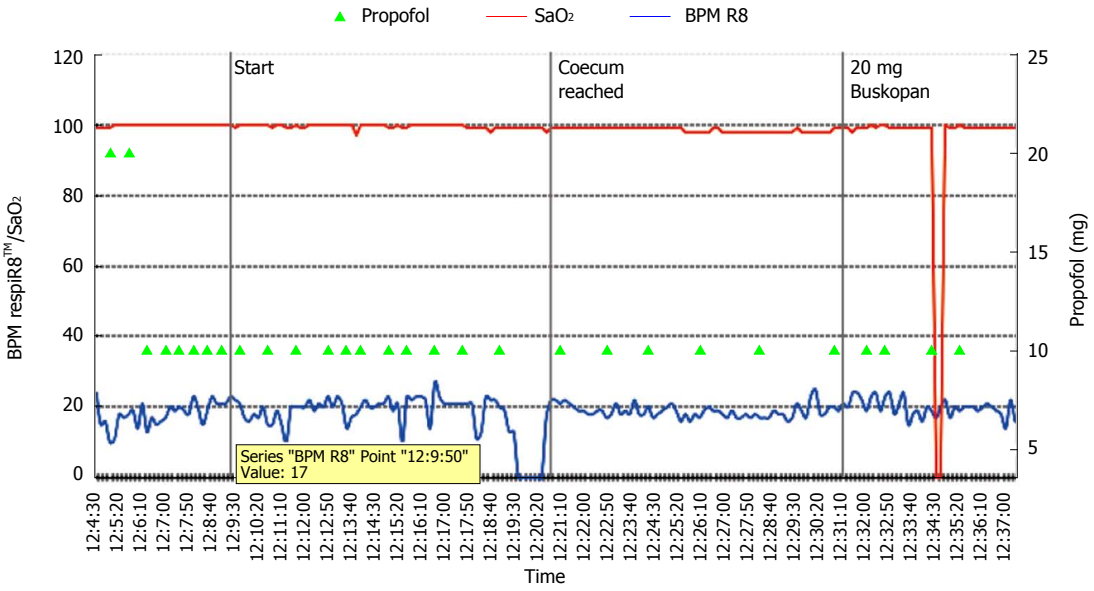

Figure 2 Typical courses of SaO_2 and RR (respir8™) showing the variability in the monitoring data. Blue line: respiratory rate (breaths/min); Red line: SaO_2 measured by pulse oximetry; Green triangles: Incremental boluses of propofol.

dependent predictor of respiratory events in our study, which confirmed the observation by Beitz *et al*[15].

Unfortunately, the respiratory rate displayed by the respiR8™ device in clinical circumstances can be impaired by artifacts. These artifacts are typically related to an involuntary slipping of the oxygen mask, which occurs with the same frequency as displacements of the fingertip sensor used for pulse oximetry. Similar artifacts were shown to occur after nasal cannula dislocation and with device dysfunction in the capnographic monitoring of ventilator activity in a study from Beitz[15].

Our study has certain limitations. We included only patients with ASA I-Ⅲ, and these findings may not hold true in ASA Ⅳ-Ⅴ patients, who have a higher risk of developing respiratory and other adverse events. Whether special subgroups of patients (*e.g.*, COPD, asthma, ASA Ⅲ-Ⅴ, obese patients) may benefit from additional monitoring should be addressed in further studies.

We conclude that apnea occurs commonly during endoscopy under sedation and most likely precedes the development of hypoxemia. The newly developed respiratory rate-monitoring device based on humidity in expired air detects more respiratory events and may provide an earlier warning of impending respiratory abnormalities that are not detected with pulse oximetry alone. We recommend using this method as an alternative to capnography in endoscopy to facilitate the earlier detection of ventilatory problems.

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COMMENTS

Background

Colonoscopies are easier and more comfortable if they are performed under sedation. Nevertheless, the use of sedative agents can lead to cardiopulmonary complications, most notably incidents of apnea.

Research frontiers

Pulse oximetry and capnography, the widely established monitoring techniques to prevent oversedation or apnea, are inaccurate and/or expensive. There is a significant need for the development of newer monitoring devices.

Innovations and breakthroughs

In this pilot-study, the authors demonstrate the feasibility of breath monitoring with a newly developed respiratory rate-monitoring device that measures the moisture in exhaled breath.

Applications

The device is easy to use in any endoscopy suite.

Peer review

A good pilot study requires a larger sample size to validate this new respiratory rate monitor under propofol sedation. The authors detected 73 respiratory events in a cohort of 76 patients. This is most likely due to the use of bolus doses of propofol. It would be more prudent to administer propofol *via* a target controlled infusion pump that would not produce peaks and valleys in the therapeutic plasma propofol level.

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BRIEF ARTICLE

Prospective postsurgical capsule endoscopy in patients with Crohn's disease

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Abstract

AIM: To clarify the usefulness of postsurgical capsule endoscopy (CE) in the diagnosis of recurrent small bowel lesions of Crohn's disease (CD).

METHODS: This prospective study included 19 patients who underwent ileocolectomy or partial ileal resection for CD. CE was performed 2-3 wk after surgery to check for the presence/absence and severity of lesions remaining in the small bowel, and for any recurrence at the anastomosed area. CE was repeated 6-8 mo after surgery and the findings were compared with those obtained shortly after surgery. The Lewis score (LS) was used to evaluate any inflammatory changes of the small bowel.

RESULTS: One patient was excluded from analysis because of insufficient endoscopy data at the initial CE. The total LS shortly after surgery was 428.3 on average (median, 174; range, 8-4264), and was ⩾ 135 (active stage) in 78% (14 of 18) of the patients. When the remaining unresected small bowel was divided into 3 equal portions according to the transition time (proximal, middle, and distal tertiles), the mean LS was 286.6, 83.0, and 146.7, respectively, without any significant difference. Ulcerous lesions in the anastomosed area were observed in 83% of all patients. In 38% of the 13 patients who could undergo CE again after 6-8 mo, the total LS was higher by ⩾ 100 than that recorded shortly after surgery, thus indicating a diagnosis of endoscopic progressive recurrence.

CONCLUSION: Our pilot study suggests that CE can be used to objectively evaluate the postoperative recurrence of small bowel lesions after surgery for CD.

Key words: Crohn's disease; Postoperative recurrence; Capsule endoscopy; Lewis score; Small bowel

Core tip: The usefulness of capsule endoscopy (CE) in diagnosing recurrent small bowel lesions after surgery for Crohn's disease (CD) has not yet been sufficiently established. This study revealed that many inflammatory lesions were already present throughout the residual small bowel shortly after surgery for CD, thus indicating an active stage of the disease on the basis of the total Lewis score in 77.8% of the patients. We concluded that the CE findings shortly after surgery can be used as a baseline for comparison against the findings from

additional CE sessions over time and that this method can be used to objectively evaluate the postoperative recurrence of small bowel lesions after surgery for CD.

Kono T, Hida N, Nogami K, Iimuro M, Ohda Y, Yokoyama Y, Kamikozuru K, Tozawa K, Kawai M, Ogawa T, Hori K, Ikeuchi H, Miwa H, Nakamura S, Matsumoto T. Prospective postsurgical capsule endoscopy in patients with Crohn's disease. *World J Gastrointest Endosc* 2014; 6(3): 88-98 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i3/88.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i3.88

INTRODUCTION

Crohn's disease (CD) is a chronic progressive idiopathic inflammatory bowel disease that is characterized by lesions that can potentially affect the entire digestive tract. CD is likely to be complicated by stenosis, fistula, abscess, and other intestinal abnormalities, requiring surgical resection of the intestine in approximately 75% of all patients[1-3]. Although the pathophysiology of CD is increasingly understood and treatments with biological agents have advanced remarkably, the rate of small bowel resection has remained unchanged from that recorded 10 years ago[4].

One of the important issues in the management of CD is that the surgical resection of lesions is not compatible with radical treatment, and postoperative recurrence is observed in a high percentage of patients. Endoscopic recurrence primarily occurs at the site of the ileocolonic anastomosis and the neoterminal ileum, and is detected before clinical recurrence occurs. The incidence of endoscopic recurrence is 70%-73% at 3 mo, 72%-93% at 1 year, and 79%-100% at 3 years after surgery[5-7]. Clinical recurrence occurs in 20% at 1 year, 17%-55% at 5 years, and approximately 32%-76% at 10 years after surgery, requiring reoperation in approximately 50% of all patients during the 20-year period after surgery[3,5].

To prevent recurrence after surgery for CD, various prophylactic treatments have been attempted, such as the use of 5-aminosalicylates, immunomodulators, or antimicrobial agents. Recently, close attention has been given to anti-tumor necrosis factor (TNF) α antibody as an agent for preventing postoperative recurrence[8-10]. In evaluating the efficacy of these prophylactic therapies, it is essential to establish a diagnostic technique that enables the precise judgment of the presence of postoperative recurrence.

The current gold standard for the evaluation of postoperative endoscopic recurrence is to perform ileocolonoscopy to assess the severity of the lesions at the site of the ileocolonic anastomosis and the neoterminal ileum according to the Rutgeerts score[5]. However, this method, poses several problems. Ileocolonoscopy is an invasive procedure that often requires sedation and analgesia. Therefore, the tolerability of the procedure is an important problem if such an examination is repeatedly performed over time in patients under postoperative clinical remission. Furthermore, the insertion of the endoscope to the ileocolonic anastomosis is sometimes difficult because of adhesions and may not always be successful. Even in cases where the endoscope has reached the anastomosed site, only a limited area of the distal part of the small bowel is observable. Furthermore, we cannot rule out the possibility that inflammatory lesions detected by ileocolonoscopy in the neoterminal ileum within 1 year after surgery represents lesions that were left unresected during the operation (rather than new lesions that developed after surgery). In patients who underwent operative procedures other than ileocecal resection, *e.g.*, partial small bowel resection or ileostomy, it is difficult to evaluate the postoperative recurrence affecting the residual small bowel using colonoscopy.

Capsule endoscopy (CE), a diagnostic imaging tool for the small bowel, is characterized by its less invasive nature and its capability to observe the entire small bowel. CE has been shown to be superior over other radiologic and endoscopic modalities, such as small bowel follow-through, computerized tomographic enterography, ileocolonoscopy, and push enteroscopy, in terms of the effectiveness in diagnosing small bowel lesions associated with the non-stricturing type of CD[11]. However, the usefulness of CE in diagnosing recurrent small bowel lesions after surgery for CD has not yet been sufficiently established[12-14].

The present study, had the following objectives: (1) to use CE to prospectively evaluate the presence/absence, location, and severity of inflammatory lesions in the entire residual small bowel of CD patients shortly (within 1 mo) after the surgical resection of macroscopic lesions; and (2) to perform CE again approximately 6 mo after surgery to compare the findings with those obtained shortly after surgery, with the goal of examining whether it is possible to judge the presence of progressive recurrence in the small bowel and the efficacy of postoperative prophylactic treatments.

MATERIALS AND METHODS

Ethical considerations

The protocol for this study was prepared in compliance with the Declaration of Helsinki and the Ethical Guidelines on Clinical Studies, and was approved by the Ethics Committee of our university.

CD patients

This study was carried out as a single-center prospective study at the Hyogo College of Medicine (Hyogo, Japan) between November 2009 and December 2011. The inclusion criteria were as follows: (1) patients aged ⩾ 16 years with a definitive diagnosis of ileal-type or ileocolonic-type CD; (2) patients who had undergone ileocolonic or ileal resection for the treatment of CD-related lesions within the previous 1 mo; (3) patients in whom the lesions detected *via* preoperative evaluations or

Table 1 Clinical characteristics of patients (n = 19)

Characteristics	Statistics
Age (yr)	37.6 ± 10.2
Gender (male/female)	14/5
Duration of CD (yr)	13.5 ± 10.6
Smoking (yes/no)	2/17
Disease location	
Ileum only	4
Ileum and colon	15
Disease behavior (B1/B2/B3)	2/6/11
Surgical resection (times)	
1	6
⩾ 2	13
Type of surgery	
Ileocolonic resection	16
Partial ileal resection	3
Ileostomy	7
Length of the residual small intestine (cm)	455 ± 52
Preoperative medications	
Mesalamine	15
Elemental diet	12
Corticosteroids	6
Immunomodulators	1
Anti-TNFα antibody	4

Data are shown as the mean ± SD or number. Disease behavior was rated according to the Montreal classification: B1: Nonstricturing, nonpenetrating; B2: Stricturing; B3: Penetrating; TNF: Tumor necrosis factor; CD: Crohn's disease.

surgical inspection of the serosal surface had been completely resected, leaving no evident residual lesion; and (4) patients who fulfilled the above 3 criteria regardless of a history of colonic resection or the presence/absence of ileostomy. The exclusion criteria were as follows: (1) patients who had undergone stricture-plasty without the resection of narrowed small bowel lesions; (2) patients in whom macroscopically evident small bowel lesions were left unresected during surgery; (3) patients in whom the evaluation of the residual small bowel was difficult intraoperatively because of adhesion and other issues; and (4) patients judged by the attending physician as being inappropriate for the study. Informed consent was obtained from each eligible patient.

CE was performed shortly after surgery on 19 patients with CD who satisfied the criteria. Table 1 summarizes the clinical characteristics of these 19 patients. The operative procedure was ileocolonic resection (including previous anastomosis) in 16 patients and partial ileal resection in 3 patients. Of the patients who underwent ileocolonic resection, 7 required ileostomy. Anastomosis had been performed on 12 patients (8 ileocolonic anastomosis, 2 ileo-ileal anastomosis, and 2 ileocolonic anastomosis + ileo-ileal anastomosis). The mean length of the residual small bowel, measured intraoperatively, was 455 ± 152 cm. The CRP level at the time of CE was 0.26 ± 0.54 mg/dL. In 10 patients, excluding those who underwent ileostomy, the CD activity index (CDAI) was 161.66 ± 55.36.

CE shortly after surgery: methods

CE was carried out with a Given PillCam SB system (Given Imaging Limited, Yoqneam, Israel). Because patients with evident residual stenosis found during open abdominal surgery were excluded from this study, no evaluation to verify the absence of stenosis was made prior to CE. All patients had undergone surgery within the previous 1 mo, and all of them received CE during the postoperative hospital stay.

Each patient fasted for 12 h or more, before the examination. A capsule endoscope was taken orally with 100-200 mL water. To improve the image quality and to ensure the visualization of the entire small bowel, an isotonic magnesium citrate solution (500 mL) combined with 2 mL dimethicone was orally administered in 5 divided doses at intervals of 30 min after swallowing the capsule[15]. The ingestion of clear liquids was permitted after finishing the intake of the isotonic magnesium citrate solution. During CE, symptoms such as discomfort reported by the patient, and the presence of adverse events (*e.g.*, capsule retention) were recorded. The data were collected approximately 8 h later for image analysis.

CE assessment

The images were analyzed using the RAPID® 6.5 ACCESS software (Given Imaging Limited). In cases where the ileocolonic anastomosis was confirmed or capsule excretion into the ileostomy was definitely confirmed, a judgment of "observation of the entire residual small bowel possible" was made. Each CE image was evaluated by an experienced gastroenterologist (T.K.) familiar with the examination of inflammatory bowel disease and with CE evaluation. For each patient, the CE images were evaluated in detail over a period of 2 h on average.

The Lewis score (LS) was used as the scoring index to quantify the inflammatory small bowel lesions detected *via* CE[16]. The area from the duodenal bulb to the site of the ileocolonic anastomosis or ileostomy was divided into 3 equal portions (proximal, middle, and distal tertiles) according to the transition time, and the score for each tertile was determined. In cases where a lesion was found at the site of the ileocolonic anastomosis, it was reflected into the score for the distal tertile. The total LS was defined as the edema and ulcer score of the most severe tertile plus the stenosis score. Activity was rated according to the criteria given in the original paper on total LS: no disease (score, < 135), mild disease (135-790), or moderate to severe disease (> 790). In our study, aphthae or erosion was defined as small mucosal breaks of approximately ⩽ 3 mm, and was evaluated separately from ulcers. The number of aphthae or erosions and the distribution of these lesions were measured in each patient.

Follow-up

CE was performed again approximately 6-8 mo after surgery to evaluate the changes in the small bowel lesions through a comparison with the CE findings recorded shortly after surgery.

Because the use of a patency capsule had not been approved in Japan during the study period, conventional small bowel enteroclysis was carried out in advance in

all patients to exclude those with small bowel stenosis or proximal bowel dilatation from the study.

The follow-up CE was carried out in a similar way to the CE conducted shortly after surgery. An evaluation was made in terms of the LS and the number of aphthae or erosions. The difference between the total LS shortly after and 6 mo after surgery was calculated as ΔLS. The ratings used a 3-category scale: progressive recurrence (total LS higher by 100 or more than the score recorded shortly after surgery), improved (total LS lower by 100 or more than the score recorded shortly after surgery), or unchanged (total score changed by -99 to +99 compared with that recorded shortly after surgery).

Ileocolonoscopy was also performed on patients who underwent ileocolonic resection within 14 d following the follow-up CE procedure. For each patient, a gastroenterologist who was blind to the findings of CE performed ileocolonoscopy. Postoperative endoscopic recurrence in the neo-terminal ileum and the ileocolonic anastomosis was evaluated using the Rutgeerts score (RS)[5]. The details of RS are as follows: i0 (no lesions), i1 (< 5 aphthous lesions), i2 [diffuse aphthous lesions with normal mucosa between lesions, or skip areas of larger lesions confined to the ileocolonic anastomosis (< 1 cm in length)], i3 (diffuse aphthous ileitis with diffusely inflamed mucosa), or i4 (diffuse inflammation with large ulcers, nodules, and/or narrowing). A RS of 2 or more was defined as endoscopic recurrence.

Statistical analysis

Continuous variables were expressed as the mean and standard deviation, or mean and median plus range. Mann-Whitney's *U* test was used to test the differences between the unpaired groups. The Wilcoxon sign-rank test was used to test the differences between the paired groups. Categorical data were analyzed with Fisher's exact test. The statistical analysis was carried out using Dr. SPSS II for Windows version 11.0 (SPSS Japan Inc., Tokyo, Japan). A P value of < 0.05 was considered statistically significant.

RESULTS

Evaluation of residual small bowel lesions via CE shortly after surgery for CD

Of the 19 patients with CD who satisfied the inclusion criteria, CE was performed 17.3 ± 5.6 d after surgery on average. No CE-related adverse event was recorded in any patient, and the examination was well-tolerated.

The observation of the entire residual small bowel was possible in 18 patients (95%). In the remaining 1 patient, CE did not reach beyond the middle segment of the ileum during the 8 h of recording; thus, this patient was excluded from analysis. No adverse events (*e.g.*, delayed retention) developed later in this patient. CE was also carried out without any problems in patients who underwent ileostomy. Among the remaining 18 patients, the mean small bowel transition time was 245 ± 210.7 min.

In all 18 patients in whom the observation of the entire residual small bowel was possible, the CE procedure detected some abnormalities: edema was detected in 13 patients (72.2%), ulcers in 12 patients (66.7%), stenosis in 1 patient (5.6%), and aphthae or erosion in 16 patients (88.9%).

The total LS (the edema and ulcer score of the most severe tertile plus the stenosis score) averaged 428.3, and its median was 174 (range, 8-4264). Disease activity as rated from the total LS was as follows: no disease in 4 (22.2%) patients, mild disease in 13 (72.2%) patients, and moderate to severe disease in 1 (5.6%) patient. Thus, although the examination was conducted shortly after surgery, 14 (77.8%) patients were rated as having active disease.

An analysis of the LS for each tertile (edema + ulcer + stenosis score for each of the 3 equal portions of the residual small bowel) showed that the proximal tertile had a mean score of 286.6 and a median score of 8 (range, 0-4264), the middle tertile had a mean score of 83.0 and a median score of 0 (range, 0-337), and the distal tertile had a mean score of 146.7 and a median score of 135 (range, 0-458) (Figure 1A). Lesions were found in the entire segments of the residual small bowel, including the proximal segment, without a significant difference between any 2 tertiles.

Figure 1B and C illustrates the edema and ulcer LS for each tertile. The edema LS did not differ significantly between any 2 tertiles. The ulcer LS for the distal tertile (mean, 114.7; median, 135; range, 0-459) was significantly higher than that for the proximal tertile (mean, 107.5; median, 0; range, 0-1800) ($P = 0.027$). Stenosis was detected in 1 patient who underwent partial ileal resection. The site of stenosis in this patient was the ileo-ileal anastomosis. The capsule passed this area after a 110-min retention in the proximal side of this area.

Among 12 patients who underwent ileocolonic or ileo-ileal anastomosis (14 sites in total), 10 patients (83.3%) developed ulcers in the anastomosed area. Of the 10 sites of the ileocolonic anastomosis, 7 (70%) sites developed ulcers, 1 site was free of ulcers, and 2 sites could not be evaluated because of the presence of residues. Ulcerous lesions were noted at all 4 sites of ileo-ileal anastomosis. Excluding 1 site of ileo-ileal anastomosis, all 13 anastomosis sites were in the distal tertile.

When the ulcer LS was calculated for each tertile, (excluding the anastomotic ulcers), the mean score was 57.5, 41.7, and 32.5 for the proximal, middle, and distal tertiles, respectively, without a significant difference between any 2 tertiles. The total LS, excluding ulcers and stenosis of the anastomosed site, averaged 176.4, and its median was 112 (range, 0-1012). Disease activity as rated on the basis of the total LS, excluding ulcers and stenosis of the anastomosed site, was as follows: no disease in 10 (55.6%) patients, mild disease in 7 (38.9%) patients, and moderate to severe disease in 1 (5.6%) patient. Eight (44.4%) patients had a high activity score, corresponding to mild or more

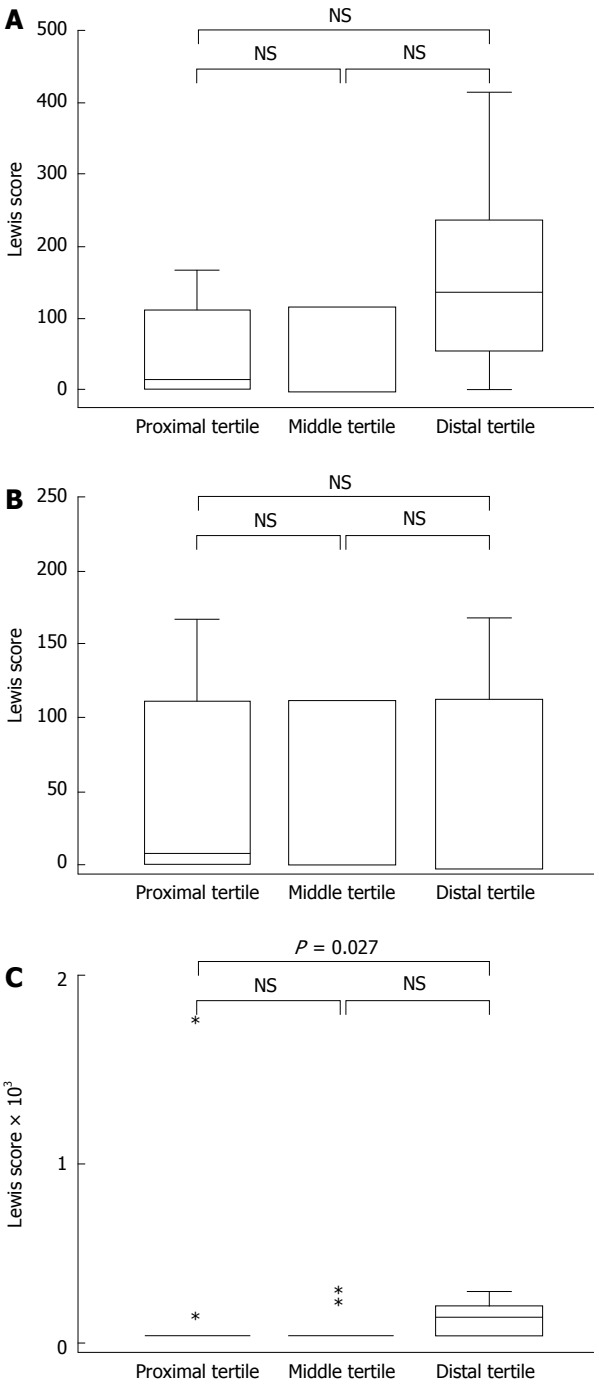

Figure 1 Lewis score (median and quartile) for each tertile of the residual small bowel, divided into 3 equal portions on the basis of the capsule endoscope transition time shortly after surgery. A: Total Lewis score (LS) (edema + ulcer + stenosis scores); B: LS for edema; C: LS for ulcers. NS: Not statistically significant difference (Mann-Whitney *U* test).

severe disease. The mean number of aphthae or erosions observed was 3.2 ± 3.9, 2.1 ± 2.5, and 1.6 ± 1.6 for the proximal, middle, and distal tertiles, respectively (Figure 2).

When analyzed in relation to clinical background variables (presence/absence of preoperative anti-TNFα antibody therapy, penetrating/nonpenetrating type, history of surgery, and presence/absence of ileostomy), none of the background variables were associated with significant

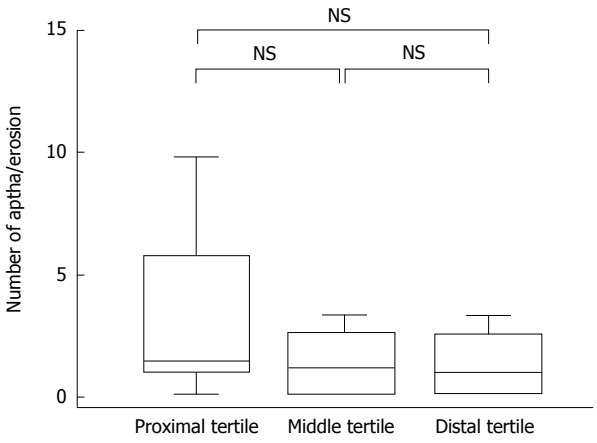

Figure 2 Number of aphthae or erosions across tertiles soon after surgery (median and quartile). NS: Not statistically significant difference.

differences in the total LS, edema/ulcer/stenosis LS, or the number of erosions.

Influence of CE findings shortly after surgery on the prophylactic treatments for recurrence

No restrictions were imposed on the postoperative treatment, which was decided through a discussion between the attending physician and each patient based on the clinical background, preoperative treatment, and early CE findings.

All 4 patients rated as having no disease based on the CE findings shortly after surgery desired to continue the 5-aminosalicylate therapy and elemental diet that had been started preoperatively. Of the 13 patients rated as having mild disease, 3 desired to continue the same therapy (5-aminosalicylates and elemental diet) and 10 desired to receive anti-TNFα antibody treatment. One patient rated as having moderate to severe disease desired to receive anti-TNFα antibody treatment.

Altogether, 8 (44.4%) of the 18 patients requested a change in their prophylactic treatment, upon being informed of the findings from the CE shortly after surgery.

Follow-up

The follow-up CE at 6-8 mo after surgery was possible in 13 of the 18 patients: 1 patient was excluded from follow-up because of the finding of a stenosed lesion in the CE shortly after surgery, and another 4 patients were excluded because they refused follow-up CE or were transferred to other facilities. The CRP level at the time of follow-up CE was 0.32 ± 0.18 mg/dL. In 7 patients, excluding those who underwent ileostomy, the CD activity index (CDAI) at the time of follow-up CE was 109.3 ± 28.34 (range, 68-139). No sign of clinical recurrence, as judged by the physician, was noted in any of these patients. Prestenosis dilatation was not detected *via* conventional small bowel enteroclysis prior to CE in any of the patients.

For the 13 patients in whom follow-up CE was possible, the total LS determined from CE findings shortly after surgery was 215.0 on average (median, 168; range,

Table 2 Changes in capsule endoscopy findings from shortly after surgery to 6-8 mo later

	CE shortly after surgery	CE 6-8 mo later	*P* value
Total LS	215:168 (8-562)	196:143 (8-450)	NS
Activity			NS
	No disease: 2 Mild disease: 11	No disease: 4 Mild disease: 9	
Edema LS			
Proximal	40.6:8 (0-168)	36.3:8 (0-112)	NS
Mid	48:0 (0-280)	9.8:0 (0-112)	NS
Distal	31.4:0 (0-168)	27.1:0 (0-112)	NS
Ulcer LS			
Proximal	10.4:0 (0-135)	41.5:0 (0-135)	NS
Mid	57.7:0 (0-300)	38.1:0 (0-225)	NS
Distal	133.8:135 (0-450)	118.8:0 (0-450)	NS
Aphthae/erosion (number)			
Proximal	3.2:1 (0-12)	4.9:2 (0-17)	NS
Mid	2.1:2 (0-9)	10.5:3 (0-40)	0.036
Distal	1.6:1 (0-4)	8.1:5 (0-18)	0.015

Data are expressed as mean: median (range) or the number of patients. LS: Lewis score. Endoscopic disease activity: no disease (total LS < 135) and mild disease (135-790). NS: Not statistically significant; CE: Capsule endoscopy; CD: Crohn's disease; LS: Lewis score.

8-562). The postoperative treatment given for these 13 patients was anti-TNFα antibody in 9 patients and 5-aminosalicylates + elemental diet in 4 patients.

The follow-up CE was performed 216.9 ± 23.6 d after surgery on average. In all patients, the follow-up CE enabled the observation of the entire residual small bowel. CE was well-tolerated, causing no adverse events such as capsule retention. The mean small bowel transition time was 132 ± 64.2 min. Edema was detected in 10 (76.9%) patients, ulcers in 9 (69.2%), and stenosis in none of the patients. Aphthae or erosion was detected in all 13 patients.

Table 2 compares the findings from CE performed shortly after surgery with those from the follow-up CE in the 13 patients. The total LS at the follow-up CE was 196.1 on average (median, 143; range, 8-450), without a significant difference from the LS recorded shortly after surgery. Furthermore, in terms of the edema and ulcer LS for each tertile, there were no significant differences between the data from shortly after surgery and those from follow-up CE. The number of aphthae or erosions in the middle and distal tertiles was significantly larger at the time of follow-up than that recorded shortly after surgery ($P = 0.036$ and $P = 0.015$, respectively).

A total of 9 anastomosed sites were observed in 8 patients (ileo-ileal anastomosis at 2 sites and ileocolonic anastomosis at 7 sites). During the follow-up CE, observation was possible at all anastomosed sites, revealing active ulcers at 6 sites (66.7%), and scarring of the ulcers at 2 sites.

Of the 4 patients who underwent ileostomy, 3 had a total LS of ⩾ 135 (corresponding to the active stage of the disease) according to the CE findings shortly after surgery. Of these 3 patients, only 1 was rated as having active disease at the time of follow-up.

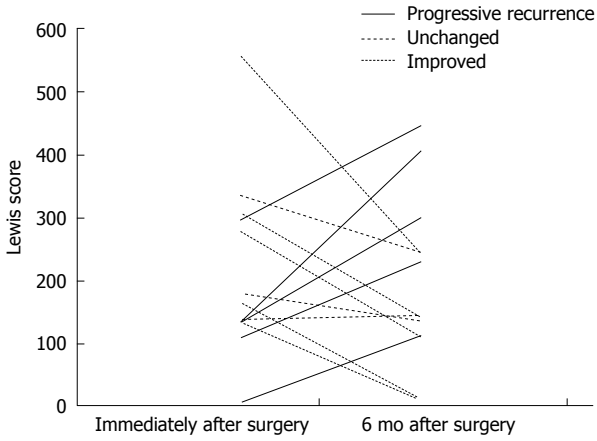

Figure 3 Changes over time in the total Lewis score from the time shortly after surgery to 6-8 mo later (*n* = 13). The total Lewis score (LS) increased by 100 or more (corresponding to progressive recurrence) in 5 patients, decreased by 100 or more (improved) in 5 patients, and changed by -99 to +99 (unchanged) in 3 patients.

When the total LS at the time of follow-up was compared with the total LS shortly after surgery (ΔLS) in each patient, there were 5 patients in whom the score had increased by 100 or more (rated as progressive recurrence), 5 patients in whom the score decreased by 100 or more (rated as improved), and 3 patients in whom the score changed by -99 to +99 (rated as unchanged) (Figure 3). Figure 4 is a graphical comparison of the changes in total LS between the 9 patients who received postoperative anti-TNFα antibody treatment and the 4 patients who were not given anti-TNFα antibody. In the anti-TNFα antibody treatment group, the change was rated as progressive recurrence in 4 patients, improved in 4 patients, and unchanged in 1 patient. In the group without anti-TNFα antibody treatment, the change was rated as progressive recurrence in 1 patient, improved in 1 patient, and unchanged in 2 patients. Thus, in this study, the change in LS did not differ according to the presence or absence of the postoperative use of anti-TNFα antibody.

Ileocolonoscopy was also performed on all 6 patients who underwent ileocolonic resection. According to the RS, 3 patients (50%) showed endoscopic recurrence in the neo-terminal ileum and the ileocolonic anastomosis (Table 3). The mean ulcer LS of the follow-up CE in the distal tertile were 0, 217 ± 116.7, and 295 ± 157.6 in patients with Rutgeerts scores (RS) of 0, 1, and 2, respectively. The assessment results for the presence or absence of endoscopic recurrence based on RS were consistent with those based on ΔLS in 4 (67%) of 6 patients. In Case 3, (1 of the 2 patients with inconsistent assessment results), recurrence was determined *via* ΔLS, whereas no recurrence was determined by *via* RS because only a limited area of the neo-terminal ileum was observable by using ileocolonoscopy. In Case 4, the total LS was high shortly after surgery and showed improvement 6 mo later. However, recurrence was determined *via* RS because some lesions remained in the neoterminal ileum.

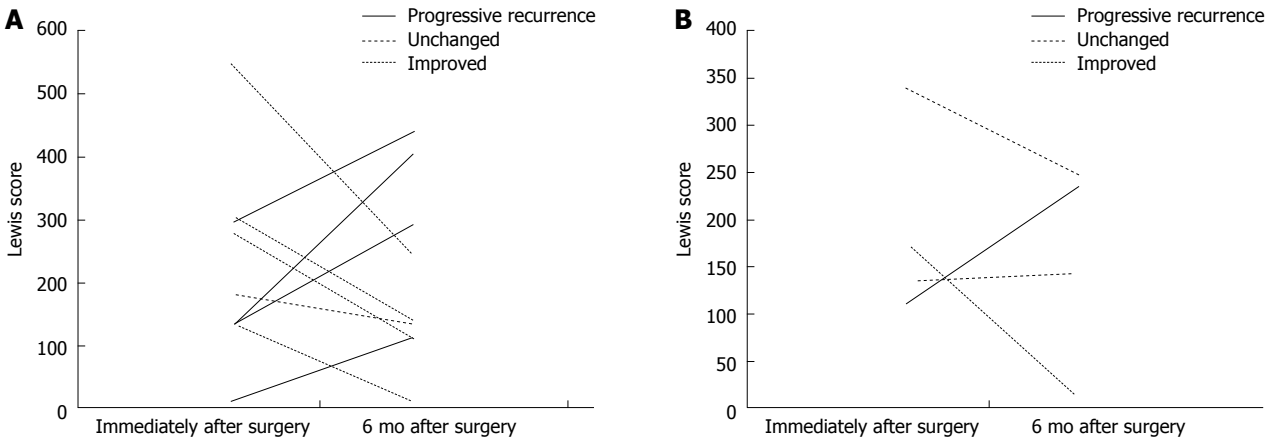

Figure 4 Changes in the total Lewis score from shortly after surgery to 6-8 mo later, analyzed in relation to the postoperative treatment. A: In the anti-tumor necrosis factor (TNF) α antibody treatment group (n = 9), the rating was progressive recurrence in 4 patients, improved in 4 patients, and unchanged in 1 patient; B: In the group without anti-TNFα antibody treatment (n = 4), the rating was progressive recurrence in 1 patient, improved in 1 patient, and unchanged in 2 patients.

Table 3 Comparison of postoperative endoscopic recurrence detection by ileocolonoscopy and capsule endoscopy in 6 patients who underwent ileocolonic resection

Cases	Ileocolonoscopy	Capsule endoscopy			
	Rutgeerts score	Ulcer LS: 6-8 mo later (distal tertile)	A: Total LS shortly after surgery	B: Total LS: 6-8 mo later	ΔLS (B-A)
1	0	0	135	8	-127
2	1	135	278	135	-243
3	1	300	135	412	277 (recurrence)
4	2 (recurrence)	135	308	142	-166
5	2 (recurrence)	300	135	300	165 (recurrence)
6	2 (recurrence)	450	300	450	150 (recurrence)

ΔLS: Changes in total LS from shortly after surgery to 6-8 mo later. LS: Lewis score.

DISCUSSION

To our knowledge, this study was the first to attempt to evaluate small bowel lesions by using CE in patients shortly after surgery for CD. We believe that the evaluation of the presence/absence and severity of lesions in the entire residual small bowel shortly after surgery for CD could be an important step in postoperative endoscopic surveillance.

In patients with CD, intestinal complications such as obstruction, stenosis, abscess, fistula, and perforation, often serve as surgical indications[17]. These factors also make it difficult to perform a sufficient preoperative evaluation of the distribution and severity of small bowel lesions. As a result, surgeons are sometimes forced to check for the presence of lesions macroscopically during open abdominal surgery. In a previous study where intraoperative endoscopy was used to observe the entire small bowel in a retrograde manner from the distal end of the dissected intestine, lesions such as edema, redness, and ulcers were observed in 65% of all cases, and more than half of these lesions were not detected using preoperative radiography or surgical inspection of the serosal surface[18]. Thus, it has been reported that even when the surgical resection was considered radical or curative, the possibility of the presence of residual lesions was not low[19].

Bearing this in mind, we performed CE shortly after surgery (17 d after surgery on average) in patients with CD who had been intraoperatively judged to have no evident residual lesions in the small bowel. This evaluation revealed that lesions such as edema, ulcers, stenosis, aphthae, and erosions were already present in the entire residual small bowel shortly after surgery, enabling a judgment of an active stage of the disease based on the total LS in 77.8% of all patients.

Among others, the ulcer LS was particularly high in the distal tertile (corresponding to the neoterminal ileum, which is most likely to develop postoperative recurrence) shortly after surgery. This result appears to reflect the influence of ulcerous lesions left unresected during surgery and the presence of ulcers that developed in the anastomosed site. CE shortly after surgery revealed ulcers at anastomosed sites in 83.3% of the patients who underwent anastomosis. In the past, ulcerous lesions at the anastomosed sites detected using ileocolonoscopy at 6-12 mo after surgery were considered to represent a recurrence of CD[5]. However, our findings from CE shortly after surgery suggested that the ulcers at the anastomosed sites do not represent lesions recurring at a certain time after the surgery but are formed at a very early period after the surgery, due to factors such as responses of the anastomosed site to suturing or a disturbed blood flow[7,20], which could, in some cases, persist for an ex-

tended duration without complete healing. Furthermore, in using CE shortly after surgery, we found ulcers that formed at the site of the ileo-ileal anastomosis after partial small bowel resection (a site that is difficult to evaluate *via* ileocolonoscopy), indicating that CE is also useful in evaluating such lesions.

Even when ulcers and stenosis at the anastomosed sites were excluded, the total LS in 44.4% of all patients corresponded to the active stage. Although we cannot completely rule out that these small bowel lesions represent new lesions that developed shortly after surgery, it appears likely that many of these lesions are residual lesions that were left unresected during the operation. According to many of the recently published reports, the judgment about the presence of endoscopic recurrence after surgical treatment of CD is based on the evaluation of the neoterminal ileum *via* ileocolonoscopy at 6-12 mo after surgery. However, the term "recurrence" can be used only in cases where the lesions had been completely resected during surgery and remission was endoscopically demonstrated. Although checking for the absence of lesions at the ileal end using intraoperative endoscopy has also been proposed[7], it is not practically feasible to resect all active lesions detected *via* intraoperative endoscopy, due to the prevailing principle for the surgical treatment of CD (*i.e.*, the extent of resection should be minimized by focusing on the major lesions). Therefore, it could be hypothesized that many lesions are left unresected during surgery, as shown by the results of the present study.

The ulcerous lesions detected *via* CE shortly after surgery were also often observed at the follow-up CE performed 6-8 mo later, regardless of the postoperative treatment used to prevent recurrence. The ulcer LS in the distal tertile showed no significant changes at the follow-up from the score recorded shortly after surgery. In view of the reports published to date, it is beyond doubt that the anastomosed site and the neoterminal ileum are the primary sites for postoperative recurrence. However, the possibility remains that the lesions detected at these sites could include diverse lesions not confined to true recurrent lesions that developed after surgery, for example, residual lesions that were left unresected during surgery (which either became aggravated or remained unchanged after surgery) or anastomotic ulcers that formed shortly after surgery and persisted.

The inflammatory lesions detected *via* CE shortly after surgery were observed in both the proximal and distal parts of the small bowel at a similar frequency. In the past, the frequency of proximal small bowel lesions in patients with CD was reported to be approximately 5%[21]. However, this frequency was based on radiographic diagnosis, and the use of CE has resulted in the detection of lesions in the proximal small bowel at a frequency of approximately 50%[22]. Furthermore, in a study involving CE in patients with CD at 3-6 mo after ileocolonic resection, a similar frequency (50%-56%) of proximal small bowel lesions was reported[12], in accordance with the results from the present study. According to a previous report, lesions found in the proximal small bowel are unlikely to be associated with clinical symptoms[22]. However, CD cases in which lesions developed in the proximal small bowel postoperatively have been reported, although the frequency of these lesions is not certain[23]. In the future, a long-term prospective survey with the use of CE may reveal the clinical significance and the natural history of the lesions found in the proximal small bowel after surgery for CD.

To date, only 3 reports have been published on the CE evaluation of recurrent small bowel lesions during the early postoperative period in CD patients[12-14]. In all 3 reports, the evaluation of endoscopic recurrence within 1 year after ileocolonic resection was performed by comparing the findings from ileocolonoscopy and CE; however, no consensus was reached regarding the usefulness of CE. In these studies, CE evaluation was done at only 1 time point after surgery. For an accurate evaluation of recurrent lesions after the surgical treatment of CD, it is necessary to repeat the test at multiple time points and, beginning shortly after surgery. With this in mind, we carried out CE at 2 time points (soon after surgery and half a year after surgery) and evaluated recurrence on the basis of changes in CE findings from the baseline to the second CE session. Patients showing a marked increase (by 100 or more) in the total LS during this period were rated as having "progressive recurrence" (the development of new lesions or aggravation of residual lesions). With this evaluation method, endoscopic progressive recurrence was noted in 5 of the 13 patients (38.5%), including 4 patients who received postoperative treatment with anti-TNFα antibody, a therapy previously reported to be highly effective in suppressing postoperative recurrence. This discrepancy in the results between the present study and the previously reported studies may be due to the following factors: (1) CE can be used to evaluate not only the neoterminal ileum but also the lesions remaining throughout the entire small bowel; (2) CE can be used to detect edema as a lesion, but edema is not covered by the Rutgeerts score; (3) the present study included patients who had used anti-TNFα antibody before surgery; and (4) the present study included patients who underwent ileostomy.

Our study had a limited number of patients in whom direct comparisons could be performed between the endoscopic recurrence results determined using RS based on ileocolonoscopy and ΔLS based on CE. However, it was suggested that CE performed at multiple time points could enable a more objective diagnosis of postoperative endoscopic recurrence of CD than ileocolonoscopy, especially in patients with several residual inflammatory lesions shortly after surgery or those with lesions located outside the ileocolonoscopy. A similar study needs to be conducted in a larger number of patients.

In the present study, CE enabled the evaluation of small bowel lesions not only in patients who underwent ileocolonic resection but also in those who underwent partial ileal resection or ileostomy. Moreover, a previous

study reported that in patients who underwent ileostomy, ileoscopy through the stoma revealed endoscopic recurrence in 70% and clinical recurrence in approximately one-third of all patients[24,25]. Therefore, CE appears to be a useful tool for the diagnosis of endoscopic postoperative recurrence in patients who underwent these operative procedures.

This study has several limitations. First, we used the LS as a scoring index for the CE evaluation of inflammatory small bowel lesions. The LS has been reported to have a higher correlation with fecal calprotectin (a marker of intestinal inflammation) than with the capsule endoscopy CD activity index[26]. However, it is unknown, whether the LS is the optimal index for the evaluation of the postoperative recurrence of CD. The LS system involves the assessment of 3 factors: edema, ulcer, and stenosis. However, this scoring index assumes a high score in cases where edema is intense. Because edema could be a nonspecific sign of an inflammation that is not associated with CD, it remains controversial whether patients presenting with edema as a major symptom could be judged as having residual or recurrent lesions. Furthermore, aphthae, a factor evaluated in the Rutgeerts scoring system, is not evaluated in the LS system. In our evaluation, the number of aphthae and erosions detected at the second CE session (6 mo after surgery) was higher than that recorded shortly after surgery. This issue needs to be addressed further, as does the necessity of developing a new and more specific index for CE evaluation after surgery for CD.

In the present study, no adverse events, such as capsule retention, occurred. However, according to a report by Pons *et al*[13], passage failure of the patency capsule was seen observed in 8% of the stenosed cases where the test was conducted at 6-12 mo after surgery. Such events need to be carefully monitored. In the present study, it was not possible to use the patency capsule because it has not been approved in Japan. In the future, it will be necessary to establish a safer testing procedure that, includes the use of a patency capsule prior to CE.

CD patients who require surgery despite a previous strict medical treatment may be viewed as having a high disease activity. It is therefore essential to identify patients who require postoperative treatment aimed at preventing recurrence, and to provide therapeutic intervention with appropriate timing. In cases where ileocolonoscopy reveals recurrence within 1 year after surgery, the risk for subsequently developing clinical recurrence is high[5], and such patients would likely be indicated for prophylactic treatment with biological agents[10,27]. The question remains as to which postoperative treatment should be selected for patients in whom the total LS indicates a high disease activity, as evaluated *via* CE shortly after surgery.

It is currently unknown whether the severity of inflammatory small bowel lesions detected using CE shortly after surgery is associated with a risk of subsequent clinical recurrence. However, lesions that remain in the small bowel after surgery can be viewed as being resistant to preoperative medical treatment even when the lesions may not be severe enough to require surgery. Therefore, continuing the preoperative treatment in such patients after surgery will not result in mucosal healing of the residual lesions. When dealing with patients with high disease activity detected *via* CE shortly after surgery, it may be advised to immediately apply active treatment with anti-TNFα antibody and other medications aimed to prevent clinical recurrence. The clinical observation of CE findings over a longer duration is required to evaluate the relationship between CE findings and the postoperative clinical course of CD.

In a conclusion, CE enabled the evaluation of residual lesions throughout the entire small bowel shortly after surgery, regardless of the operative procedure applied. Comparing the CE findings collected at multiple time points after surgery with the CE findings at baseline (shortly after surgery) may enable an objective evaluation of true endoscopic recurrence, the natural history of CD after surgery, and the efficacy of the prophylactic treatment postoperative recurrence.

ACKNOWLEDGMENTS

We are indebted to the late Professor Takayuki Matsumoto (died on October 21, 2012) for his support and guidance throughout our study.

COMMENTS

Background

After surgery for Crohn's disease (CD), patients often develop endoscopic inflammatory lesions before clinical recurrence occurs. The current gold standard for the evaluation of postoperative endoscopic recurrence is to perform ileocolonoscopy. However, authors cannot rule out the possibility that the inflammatory lesions detected by ileocolonoscopy in the neoterminal ileum within 1 year after surgery represents lesions that were left unresected during the operation rather than new lesions that developed after surgery. It is essential to establish a diagnostic technique that enables the precise judgment about the presence of postoperative recurrence.

Research frontiers

The usefulness of capsule endoscopy (CE) in diagnosing recurrent small bowel lesions after surgery for CD has not yet been sufficiently established. In this prospective study that included 19 patients who underwent ileocolectomy or partial ileal resection for CD, CE was performed 2-3 wk after surgery and was repeated after 6-8 mo, and the findings were compared to judge the presence of progressive recurrence.

Innovations and breakthroughs

This study revealed that many inflammatory lesions were already present throughout residual small bowel shortly after surgery for CD, thus indicating of an active stage of the disease on the basis of the total Lewis score in 77.8% of the patients. The authors concluded that the CE findings shortly after surgery can be used as a baseline for comparison against the findings from additional CE sessions over time and that this method can be used to objectively evaluate the postoperative recurrence of small bowel lesions after surgery for CD.

Applications

CE was safe, well tolerated and useful in the evaluation of entire small bowel after surgery for CD, regardless of the operative procedure applied. Comparing the CE findings collected at multiple time points after surgery with the CE findings at baseline (shortly after surgery) may enable an objective evaluation of true endoscopic recurrence, the natural history of CD after surgery, and the efficacy of the prophylactic treatment postoperative recurrence.

Terminology

CE: CE is a diagnostic imaging device for the small bowel. CE has been shown to be superior over other radiologic and endoscopic modalities, in terms of the effectiveness in diagnosing small bowel lesions associated with the non-structuring type of CD. Lewis score: Lewis score is the scoring index to quantify the inflammatory small bowel lesions detected *via* CE.

Peer review

This is an interesting study evaluate the use of CE soon after surgery and half year later. It provides important information about the history of small bowel Crohn's disease.

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CASE REPORT

Rare pancreas tumor mimicking adenocarcinoma: Extramedullary plasmacytoma

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Abstract

Neoplastic proliferation of plasma cells is called plasma cell dyscrasias, and these neoplasms can present as a solitary neoplasm or multiple myeloma. Extramedullary plasmacytoma, in particular pancreatic plasmacytoma, is a rare manifestation of multiple myeloma. Although computerized tomography is useful for the diagnosis of extramedullary plasmacytoma, there are no specific radiologic markers that distinguish it from adenocarcinoma. Histological confirmation by biopsy is necessary for accurate diagnosis and management of the tumor. Endosonography is the most sensitive method for the diagnosis of pancreatic tumors, and the use of fine needle aspiration by endosonography is associated with a lower risk for malignant seeding and complications. Here, we report a case of pancreatic plasmacytoma in newly identified multiple myeloma as diagnosed by endosonography. Endosonography is a reliable and rapid method for the diagnosis of extramedullary plasmacytoma. Therefore, endosonographic fine needle aspiration should be the first choice for histological evaluation when pancreatic plasmacytoma is suspected. Ideally, the pathology would be performed at the same site as endosonographic biopsy.

Key words: Plasmacytoma; Endosonography; Pancreatic mass; Multiple myeloma; Fine needle aspiration

Core tip: The rare condition extramedullary plasmacytoma involves the gastrointestinal tract, usually liver, in approximately 10% of cases. A role for the pancreas is particularly rare. Pancreatic tumors can be identified radiologically, although it is impossible to discriminate between extramedullary plasmacytoma and adenocarcinoma. The use of endosonographic fine needle aspiration to acquire a histological sample from the pancreatic mass to confirm diagnosis is feasible and informative even in the presence of inoperable mass image.

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INTRODUCTION

An uncommon manifestation of multiple myeloma is extramedullary plasmacytoma. It is generally localized to nasal fossa and rarely involves the pancreas. On imaging, such a pancreatic mass may mimic adenocarcinoma[1,2].

CASE REPORT

We present here a case of a 64-year-old man who was re-

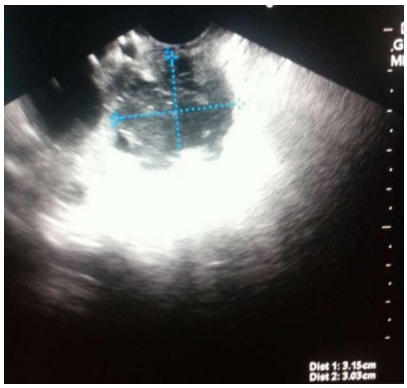

Figure 1 Endosonographic view of mass.

ferred to our endoscopy unit for endosonographic (EUS) fine needle aspiration (FNA) for a pancreatic mass.

DISCUSSION

EUS (Fujinon, Tokyo, Japan) revealed a 3 cm heterogeneous focal mass in the head of the pancreas (Figure 1). Neoplastic cells were detected by FNA (22 G; Cook Endoscopy, Winston-Salem, NC, United States), and plasmacytoma was diagnosed by the cytopathologist (Figure 2). Since plasmacytoma features are nonspecific on EUS and resemble other neoplasms including adenocarcinoma, plasmacytoma should be included in the differential diagnosis of a pancreatic mass, especially in advanced stage multiple myeloma patients. EUS-FNA is a fast and reliable technique for the diagnosis of plasmacytoma.

COMMENTS

Case characteristics

A 64-year-old man who was referred to our endoscopy unit.

Clinical diagnosis

Endosonographic (EUS) fine needle aspiration (FNA) for a pancreatic mass.

Differential diagnosis

Plasmacytoma features are nonspecific on EUS.

Imaging diagnosis

EUS revealed a 3 cm heterogeneous focal mass in the head of the pancreas. Neoplastic cells were detected by FNA, and plasmacytoma was diagnosed by the cytopathologist.

Pathological diagnosis

Since plasmacytoma features are nonspecific on EUS and resemble other neoplasms including adenocarcinoma, plasmacytoma should be included in the differential diagnosis of a pancreatic mass, especially in advanced stage multiple myeloma patients.

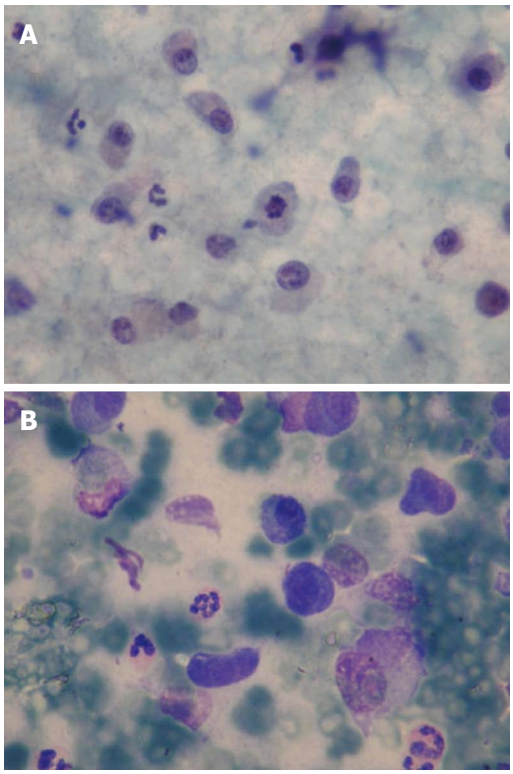

Figure 2 Cytopathologic findings of pancreatic mass obtained by endosonographic fine needle aspiration. A: Neoplasic plasmacytoid cells, mitose in the middle (× 100, Papa-nikolaou stain); B: Neoplasic plasmacytoid cells (× 100, May-Grunwald-Giemsa).

Experiences and lessons

An uncommon manifestation of multiple myeloma is extramedullary plasmacytoma. It is generally localized to nasal fossa and rarely involves the pancreas.

Treatment

EUS-FNA is a fast and reliable technique for the diagnosis of plasmacytoma.

Peer review

As mentioned in this study, extramedullary plasmacytoma is a rare presentation of multiple myeloma. So it had innovative significance for this study to report a pancreatic plasmacytoma diagnosed by EUS-FNA.

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THERAPEUTICS ADVANCES

Transumbilical laparoscopic-assisted appendectomy in children: Clinical and surgical outcomes

Nicola Zampieri, Gabriella Scirè, Alberto Mantovani, Francesco Saverio Camoglio

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Abstract

The aim of this paper is to present and describe transumbilical laparoscopic-assisted appendectomy in children, focusing on its technical aspects and clinical and surgical outcomes. The surgical charts of all patients aged between 0 and 14 years treated with transumbilical laparoscopic-assisted appendectomy admitted to the authors' institution from January 2009 to September 2013 with a diagnosis of suspected appendicitis following clinical, laboratory and ultrasound findings were reviewed. Operating time, intraoperative findings, need for conversion or for additional trocars, and surgical complications were reported. During the study period, 120 patients aged between 6 and 14 years (mean age: 9.9 years), 73 females (61%) and 47 males (39%), were treated with transumbilical laparoscopic-assisted appendectomy. There were 37 cases of hyperemic appendicitis (subserosal and retrocecal), 74 cases of phlegmonous appendicitis and 9 cases of perforated gangrenous appendicitis. It was not possible to establish a correlation between grade of appendicitis and mean operating time ($P > 0.05$). Eleven cases (9%) needed the use of one additional trocar, while 8 patients (6%) required conversion to the standard laparoscopic technique with the use of two additional trocars. No patient was converted to the open technique. Transumbilical laparoscopic-assisted appendectomy is a safe technique in children and it could be used by surgeons who want to approach other minimally invasive techniques.

Key words: Appendectomy; Children; Minimally invasive surgery; Transumbilical; Procedure

Core tip: Transumbilical video assisted appendectomy in children is safe and useful to approach minimally invasive techniques.

Zampieri N, Scirè G, Mantovani A, Camoglio FS. Transumbilical laparoscopic-assisted appendectomy in children: Clinical and surgical outcomes. *World J Gastrointest Endosc* 2014; 6(4): 101-104 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i4/101.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i4.101

INTRODUCTION

Acute appendicitis is one of the most common causes of acute abdomen in the pediatric age. A clinical approach or laboratory tests resulting in a certain diagnosis for this condition are still to be found. The surgical techniques to perform appendectomy are manifold, ranging from the widely used open technique to more innovative minimally invasive approaches such as NOTES (Natural Orifice Transluminal Endoscopic Surgery)[1].

Transumbilical laparoscopic-assisted appendectomy [TULAA], used for the first time on children during the 1990s[2-4], profited from laparoscopy to implement a new minimally invasive approach.

In 1983, Semm described the standard three-port

technique for the first time; since then, the minimally invasive approach has gained wide acceptance among pediatric surgeons worldwide[2-5]. The transumbilical laparoscopic-assisted technique (TULAA) combines the advantages of both a good intra-abdominal laparoscopic visualization and the safety and quickness of extracorporeal traditional appendectomy. In 1991, Valla *et al*[6] reported the first significant case series treated using this technique, although they were all cases of uncomplicated appendicitis. Other authors, including Ohno *et al*[7], also reported a high number of cases (more than 400 patients) with excellent results, although again all patients had uncomplicated appendicitis.

The purpose of this study is to present the cases recently treated at the authors' institution for complicated and uncomplicated appendicitis with explanation of the technique used and its technical and pre/postoperative surgical aspects.

PREOPERATIVE MANAGEMENT

At the authors' institution, all patients reporting abdominal pain with suspected appendicitis without clinical or echographic signs of complicated appendicitis are managed conservatively for the first 12 h. They receive two doses of ampicillin plus sulbactam (50 mg/kg per dose) while their symptoms are monitored and blood tests are performed before opting for either conservative treatment or surgery. The minimally invasive approach currently in use at the authors' institution is transumbilical in all cases for the camera, standard laparoscopy or TULAA.

At least 30 min before surgery, the patient's umbilicus is carefully cleansed using a cotton swab impregnated with betadine. Patients do not receive prophylactic antibiotics since they have already received antibiotic treatment.

SURGICAL PROCEDURE

The patient is placed in the supine position under general anesthesia and mechanical ventilation. Once the patient is asleep, a vesical catheter is placed; the nasogastric tube is not positioned preoperatively but only during surgery if clinically indicated. The umbilicus is disinfected again and a wide sterile surgical area prepared: operation table sheets are placed at the level of the pubo-iliac line and below the rib cage (in order to have quick direct access to the abdominal cavity in case of complications, *i.e.*, massive blood loss). The operating surgeon stands on the left side of the patient, the assistant on the right and the scrub nurse next to the operating surgeon.

The laparoscopic video display is located on the right caudal side of the patient. The access to the abdominal cavity is achieved using a vertical incision directly through the umbilicus. A 10 mm trocar is then introduced and carbon dioxide (CO_2) pneumoperitoneum pressure is maintained at 10 mmHg with a flow of 1.5 L/min. It is paramount to maintain low values of insufflation and intra-abdominal pressure in order to reduce postoperative pain and to prevent cardio-circulatory complications. A zero-degree 10 mm operative telescope is inserted for abdominal examination (Figure 1A). The operation table is placed in the Trendelenburg position and then rotated to the left. From the operating canal of the telescope, a 5 mm traumatic grasper is introduced and the CO_2 pneumoperitoneum can be increased up to 12 mmHg; flow is also increased to 2 L/min to compensate for the gas leaks. The grasper is used to identify the appendix and to dissect retroperitoneal adhesions. When the tip of the appendix is freed, it is exteriorized through the umbilicus (Figure 1B). It is important to remember that the pneumoperitoneum needs to be deflated before extracting the appendix (to reduce the space between the cecum and the abdominal cavity and to maintain a moderate traction on the mesoappendix). At this point, a standard extracorporeal appendectomy is performed (Figure 1C). With subserosal, retrocecal or complicated appendicitis, it is possible to introduce one or two additional 3-5 mm trocars for graspers or a cautery hook. The use of more than one additional trocar converts the procedure into a standard laparoscopic appendectomy.

At the end of the procedure, the trocar is inserted again for final inspection (to avoid bleeding) and, if necessary, peritoneal toilet with suction is performed (*i.e.*, with phlegmonous appendicitis or perforated appendicitis). At the end of surgery, the surgeon determines whether it is necessary to use abdominal drainage, applied as in the standard open technique or using one of the trocar ports. The fascial defect is closed with absorbable sutures. The skin suture can also be performed with absorbable stitches (Figure 1D). Naropine 0.2% local anesthetic is usually used at the site of port insertion and a bulky pressure dressing is applied over the umbilical incision.

Postoperative analgesia is administered using ketoprofen or ibuprofen. Paracetamol can also be used.

POSTOPERATIVE MANAGEMENT

If there is no perforation, therapy with the same antibiotic is continued for 24 h and then stopped, while all cases of perforated appendicitis receive a regimen of ceftriaxone (100 mg/kg per day in one single administration) plus metronidazole (7.5 mg/kg per dose every 8 h) which is continued until the patient is afebrile for at least 48 h.

Re-feeding can start 12 h after surgery with uncomplicated appendicitis, 24 h in the other cases. Patients are finally discharged from hospital if they have been afebrile for at least 24 h, have no pain and have resumed full oral diet.

CASE SERIES

The surgical charts of all patients aged between 0 and 14 years treated with TULAA admitted to the authors' institution from January 2009 to September 2013 with a diagnosis of suspected appendicitis following clinical, laboratory and ultrasound (US) findings were reviewed.

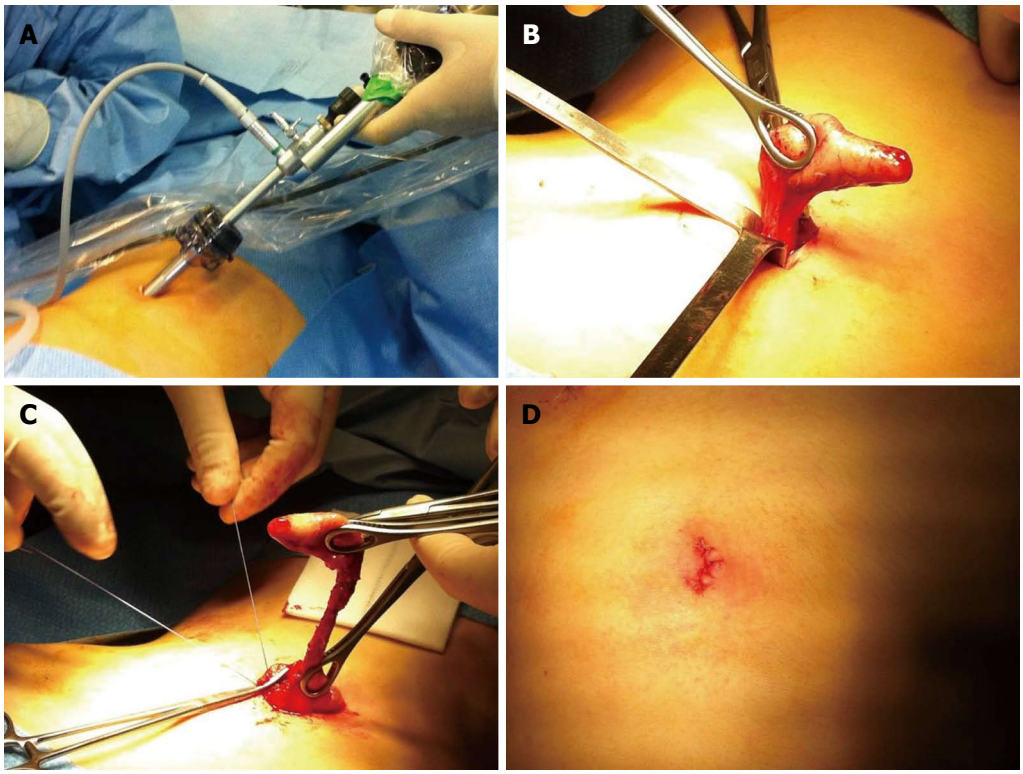

Figure 1 Surgical steps for video-assisted transumbilical appendectomy. A: Umbilical access for 10 mm port and operative camera; B: The appendix (phlegmonous) is externalized through the umbilicus; C: Open "classic" appendectomy; D: Skin closure: the umbilicus is closed with rapid 4/0 absorbable stitches.

Operating time, intraoperative findings, need for conversion or for additional trocars, and surgical complications were reported.

During the study period, 120 patients aged between 6 and 14 years (mean age: 9.9 years), 73 females (61%) and 47 males (39%), were treated with TULAA. There were 37 cases of hyperemic appendicitis (subserosal and retrocecal), 74 cases of phlegmonous appendicitis and 9 cases of perforated gangrenous appendicitis.

The grade of appendicitis was classified as reported in the literature[7]. Mean operating time was 58.6 min (range: 14-135 min), with differences depending on the grade of appendicitis: hyperemic = 55.5 min (range: 25-130 min); phlegmonous = 56.7 min (range: 14-120 min); gangrenous/perforated = 86.2 min (range: 55-135 min). It was not possible to establish a correlation between grade of appendicitis and mean operating time ($P > 0.05$). Eleven cases (9%) needed the use of one additional trocar, while 8 patients (6%) required conversion to the standard laparoscopic technique with the use of two additional trocars. No patient was converted to the open technique. Mean hospital stay was 3.7 d (range: 2-14 d). There were no cases of intraoperative complications, while postoperatively 5 patients showed umbilical infection (4%) and one patient had intra-peritoneal abscess which was managed conservatively with intravenous antibiotics.

DISCUSSION

If compared to the standard open technique, minimally invasive techniques have shown many advantages, such as easier exploration of the abdominal cavity, better diagnostic framework and differential diagnosis, as well as reduced postoperative pain. Hospital length of stay is also reduced: paralytic ileus resolves faster in patients who resume food intake early and therefore they are discharged more rapidly. In 1992, Pelosi first suggested the use of transumbilical laparoscopic-assisted appendectomy in adult patients, thus combining a laparoscopic procedure with the basic principles of the open technique and taking advantage from both the traditional and the laparoscopic approach[6-12].

TULAA was first described in pediatric patients in 1998 by C. Esposito and the first cases treated with this technique were reported by Valla *et al*[6] in 1991.

This video-assisted approach benefits from the laparoscopic technique since enlarged images allow the surgeon to observe the abdominal cavity and easily find the appendix. Also, the use of an operative optical trocar permits the introduction of graspers and cleansing instruments which are important in the most complicated cases of appendicitis. Finally, TULAA involves external appendectomy using the traditional open technique, thus reducing the length and costs of surgery.

Postoperatively, TULAA showed reduction of postoperative pain, shorter duration of pneumoperitoneum and diaphragm stimulation, and further improvement of the cosmetic result of wound scars[7,10-13].

From a technical point of view, TULAA is easier to perform than laparoscopy, with a consequently shorter learning curve for trainee surgeons. The authors' institution is a reference and excellence center for minimally

invasive surgery and their learning curve for laparoscopic appendectomy is of at least 15 surgeries, while for TULAA it is less than 10, regardless of grade of appendicitis. This is because TULAA involves a first laparoscopic approach followed by a traditional open technique for the appendectomy phase, resulting in being safe and efficient at the same time.

In the study series, 9% of cases (11 patients) required an additional port, while only 8 cases (9%) (three cases of gangrenous retrocecal appendicitis) required the placement of 2 additional trocars with conversion to the laparoscopic technique. The possibility of inserting an additional trocar in the most suitable position according to the intraoperative findings allows better management of this condition. Clearly, the learning curve with one trocar reduces surgery length as well as the need for additional trocars. In the authors' experience, higher complication rates and a more extensive use of an additional trocar occurred with this technique only during the first year of practice. It is also important to remember that TULAA is not an evolution of the laparoscopic technique; it is a different technique and surgeons with a wide laparoscopic experience also used additional trocars in the first cases treated with this technique.

There are many advantages in the use of TULAA: excellent diagnostic and therapeutic approach to the acute abdomen; observation of the entire abdominal cavity; high therapeutic reliability; high versatility; optimal cosmetic result; excellent postoperative recovery; and high feasibility, even in obese patients[13-16].

The current literature does not report real contraindications to the use of this technique apart from those generally indicated for pneumoperitoneum. As for laparoscopy, it is important to remember that insufflation pressure and flow rate must be kept as low as possible, especially in the pediatric age, in order to reduce postoperative pain. Specifically speaking for TULAA, it is necessary to deflate the abdomen before extracting the appendix since this prevents excessive traction on the mesoappendix and facilitates extraction of the appendix through the umbilicus.

CONCLUSION

According to the authors' experience, TULAA is a safe, minimally invasive approach in children suffering from acute appendicitis. It is also helpful as a training procedure for other minimally invasive approaches.

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MINIREVIEWS

Childhood achalasia: A comprehensive review of disease, diagnosis and therapeutic management

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Abstract

Achalasia is an esophageal motility disorder characterized by failure of lower esophageal sphincter (LES) relaxation and is rare in children. The most common symptoms are vomiting, dysphagia, regurgitation, and weight loss. Definitive diagnosis is made with barium swallow study and esophageal manometry. In adults, endoscopic biopsy is recommended to exclude malignancy however; it is not as often indicated in children. Medical management often fails resulting in recurrent symptoms and the ultimate definitive treatment is surgical. Laparoscopic Heller myotomy with or without an anti-reflux procedure is the treatment of choice and has become standard of care for children with achalasia. Peroral endoscopic myotomy is a novel therapy utilized with increasing frequency for achalasia treatment in adults. More experience is needed to determine the safety, efficacy, and feasibility of peroral endoscopic myotomy in children.

Key words: Achalasia; Pediatrics; Surgical Heller myotomy; Balloon dilatation; Lower esophageal sphincter

Core tip: Achalasia is a neurodegenerative disorder of the lower esophageal sphincter which occurs less commonly in children compared to adults and patients present with progressive dysphagia, vomiting, and weight loss. Medical therapy including botulinum toxin injection and endoscopic dilatation have been associated with only transient relief of dysphagia symptoms as is also seen in adults. While current evidence also suggests that the surgical approach of laparoscopic Heller myotomy provides lasting benefits for children with achalasia, future prospective evaluation will need to be conducted to ascertain whether peroral endoscopic myotomy is safe and equally effective in children.

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INTRODUCTION

Achalasia is a rare esophageal neurodegenerative disorder in the pediatric population. The disease is even more infrequent in children less than 5 years of age. The incidence of achalasia in childhood is 0.11/100000 children annually[1,2]. Overall, less than 5% of patients with symptoms present under the age of 15[3]. The disease is more prevalent in males and is most commonly idiopathic. Achalasia has been associated with Trisomy 21, congenital hypoventilation syndrome, glucocorticoid insufficiency, eosinophilic esophagitis, familial dysautonomia, Chagas' disease, and achalasia, alacrima, and ACTH insensitivity (AAA) syndrome[3].

Failure of the lower esophageal sphincter to relax

leads to the sequelae of achalasia. The pathophysiologic basis of achalasia is characterized by the degeneration of the inhibitory myenteric plexus that innervates the lower esophageal sphincter (LES) and esophageal body[4]. This leads to an imbalance in the inhibitory and excitatory neurons resulting in the failure of the LES to relax with swallowing, absence of peristalsis of the esophageal body, and increased LES resting pressures[5]. Goldblum *et al*[6] found a depletion or absence of myenteric ganglion cells, destruction of myenteric nerves, and chronic myenteric inflammation in 42 esophageal specimens. It is supposed that abnormalities in the parasympathetic innervation of the esophagus result in the esophageal dysmotility seen in achalasia; however the precise etiology of this abnormality is unclear[7].

Children usually present with progressive dysphagia, vomiting, and weight loss. Younger children and infants may also present atypically with recurrent pneumonia, nocturnal cough, aspiration, hoarseness, and feeding difficulties[3,8]. Achalasia in children is often misdiagnosed as gastroesophageal reflux disease (GERD). Children frequently present with failure to thrive, eating disorders, eosinophilic esophagitis, or asthma, which then leads to a delay in diagnosis for as long as 6-10 years[3]. Up to 50% of children are treated with antacids or prokinetics before the diagnosis of achalasia is identified[2].

DIAGNOSIS

Achalasia is diagnosed with a barium swallow study and may be confirmed with esophageal manometry. Barium swallow studies classically demonstrate a dilated esophagus with "bird's-beak" like tapering of the distal esophagus. Often, since there is a significant delay in diagnosis of achalasia in children, the esophagram study alone is diagnostic. Elevated resting LES pressure, absent or low-amplitude peristalsis, or non-relaxing LES upon swallowing are diagnostic findings on esophageal manometry in children with achalasia[1,2]. However, absence of these findings does not rule out the diagnosis of achalasia since LES function in children is heterogeneous. Partial relaxations are common and normal relaxations may also be present on manometry according to Morea *et al*[8]. Upper endoscopy and biopsy is reasonable to rule out esophagitis, Trypanosoma cruzi, malignancy, and other secondary causes of achalasia[1,4,5]. Our institutional protocol for work up consists of a barium swallow study, upper endoscopy, and endoscopic biopsy.

The various methods of treatment of achalasia involve reduction of LES pressure in order to facilitate esophageal emptying by: injection of botulinum toxin, oral administration of calcium channel blockers (Nifedipine), pneumatic dilatation, or esophageal myotomy (Heller) with or without an anti-reflux procedure.

MEDICAL THERAPY

Nifedipine, a calcium channel blocker, inhibits the trans membrane calcium influx in cardiac and smooth muscle and has been primarily used to treat achalasia in adults[5]. In children, the use of nifedipine has not been well studied. Maksimak *et al*[9] reported 4 children treated with nifedipine before meals who reported relief of symptoms likely related to a decrease in resting LES pressure. In either children or adults, nifedipine is not a definitive therapy and should only rarely be used as a bridge to relieve symptoms until pneumatic dilatation, Botox injection or myotomy can be performed[5,10].

ENDOSCOPIC THERAPY

Botulinum toxin injected into the LES acts on the excitatory terminal nerve endings of the myoneural junctions preventing acetylcholine release. Acetylcholine releasing neurons function in influencing the basal muscle tone[1]. Injection of botulinum toxin into the LES can be both diagnostic and therapeutic. Optimal dosing and injection frequency of botulinum toxin to relieve achalasia symptoms in children has not been well defined. After botulinum injection, the mean duration of symptom relief is 4 months, often requiring multiple treatments within a year[11]. In addition, botulinum toxin injection only provides permanent relief in 10%-40% of cases in adult patients[12] thus, will often require definitive surgical management.

PNEUMATIC DILATATION

Pneumatic dilatation or dilation of the functionally obstructed esophagus has been used in children. Recommended balloon sizes in children > 8 years is 35 mm[13,14]. Multiple dilatations are often required to achieve successful relief of symptoms although initial response predicts the success or failure of subsequent dilatations[15]. Hamza *et al*[14] reported a 90% success rate in children treated with multiple pneumatic dilations. The advantages of balloon dilatation include shorter length of stay, quicker recovery time, and decreased cost[13]. Pneumatic dilatation can be complicated by substernal pain, prolonged epigastric pain, esophageal perforation, aspiration pneumonia, and GERD[13,16-19]. Multiple studies suggest that in older children, pneumatic dilation is effective and safe initial treatment for achalasia and may spare children with achalasia an operation[13,14,20]. There are no long-term follow up studies in children to document success rates of pneumatic dilatation for achalasia. For adult patients, Eckardt *et al*[21] reported recurrence rates in as high as 60% in patients who underwent a single pneumatic dilation. Recurrent symptoms in children following multiple dilatations may require surgical myotomy[17,18,22].

SURGICAL

Despite multiple treatments for achalasia, surgery is the most definitive and successful treatment of choice. Laparoscopic Heller myotomy (LHM) involves making

Table 1 Patient demographics

	Mean	
Gender		
Female	13	54%
Male	11	46%
Age of diagnosis	11	5-18
Duration of symptoms	2.8 years	1-11 years
Presenting symptoms	*n*	Percentage
Dysphagia	20	83%
Emesis	14	58%
Weight loss	11	46%
Chest pain	10	42%
Regurgitation	4	17%
Odynophagia	2	8%

Table 2 Surgical approach

	Mean	
Age at surgery	12.9	5-8
OR time	124 min	45-213 min
LOS	2.7 d	1-6 d
Follow up	3.5 mo	1-12 mo
	n	Percentage
LHM	3	12.50%
LHM + TF	2	8.30%
LHM + DF	19	79.20%

LOS: Length of stay; LHM: Laparoscopic Heller myotomy; TF: Thal fundoplication; DF: Dor fundoplication.

a longitudinal incision in the muscle of the esophagus approximately 5 cm above the esophagogastric junction and extending 2-3 cm onto the cardia of the stomach. Laparoscopic Heller myotomy in children as in adults is the surgical treatment of choice[20,23-26].

Over the last 8 years at our institution, 24 patients were diagnosed with achalasia that subsequently underwent surgical treatment. Forty-six percent of the patients were male with a mean age of 11 (5-18 years). (Table 1) In this patient population, associated comorbidities included: mixed connective tissue disease scleroderma (1); Down's syndrome (1); inflammatory bowel disease (1); Sjogren's syndrome; and Pott's disease (1). The most common presenting symptoms were dysphagia (83%), emesis (58%), weight loss (46%), and chest pain (42%). Average weight loss was 9.9 kg requiring supplemental nutrition. Mean duration of symptoms prior to surgical treatment was 2.8 years, which was consistent with multiple studies[16,26-31]. Upper endoscopy in our patients commonly showed a dilated esophagus with retained food products. Approximately one-third of our patients had an abnormal biopsy. Four patients had acute esophagitis one of which was treated for Candida. Esophageal manometry was done in only 38% of our patients secondary to inability to tolerate the procedure. Only 2 patients (8%) who underwent myotomy were treated with nifedipine with only temporary relief of symptoms. Four underwent pneumatic dilatation (17%). In 1 patient, pneumatic dilatation was complicated by esophageal perforation requiring video-assisted thoracoscopic surgery (VATS) drainage and prolonged hospital stay. This patient subsequently underwent a laparoscopic Heller myotomy (LHM) and Dor fundoplication with resolution of symptoms of achalasia at 3 month follow up. Most of our patients (88%) underwent laparoscopic Heller myotomy with a Dor or Thal fundoplication. Average age at the time of surgical treatment was 12.9 years of age (5-18) (Table 2). Average operating time was 124 min.

In our series, we had only 2 intraoperative mucosal perforations, which were repaired primarily laparoscopically in children that had had LHM without fundoplication. Two children who had LHM with Thal fundoplication developed recurrent dysphagia requiring pneumatic dilations several months later. One patient who underwent a LHM and Dor fundoplication required a laparoscopic redo LHM and Dor for recurrent dysphagia. All of our patients receive a barium swallow study and a clear liquid diet on the first postoperative day. We have had no incidence of leak on the esophagram in our patients postoperatively or delayed perforations. We routinely discharge our patients on postoperative day 2 and our average length of stay is 2.6 d. Eight percent of our patients had recurrent symptoms of dysphagia postoperatively. One patient required revision of the initial operation 10 mo after the first operation (Table 3). There was a significant improvement in symptoms after the second procedure. As seen in other centers, most patients with recurrent dysphagia after surgical treatment for achalasia undergo balloon dilatation with improvement in their symptoms (Table 3).

The laparoscopic approach is superior to the open approach secondary to the well-recognized benefits including minimal pain, better cosmesis, shorter hospital stay, and faster return to normal activity for the child and parent/guardian[26]. Common causes of surgical failure are GERD and recurrent dysphagia. A partial fundoplication is commonly used to prevent GERD in patients following Heller myotomy. In a randomized controlled trial, Rebecchi *et al*[32] determined that laparoscopic Dor fundoplication after a LHM was superior to Nissen fundoplication because the recurrence rate of dysphagia was significantly higher in patients who received a Nissen fundoplication in their adult patients. There is some controversy as to whether an anti-reflux procedure should be performed in children at the time of LHM. Corda *et al*[24] concluded that an anti-reflux procedure is not required with a LHM for the prevention of GERD. Other studies have shown benefits and it is our practice to perform LHM and partial fundoplication[27,28,31,33].

The two primary complications of surgical management of achalasia are esophageal perforation and recurrent dysphagia. In our experience and review of

Table 3 Surgical management of pediatric achalasia

Ref.	*n*	Age (yr)	Symptom duration (mo)	Procedure	OR time (min)	Complications	Treatment	Length of stay (d)	Follow up (mo)
Pastor *et al*[16]	40	12.4	10.7	6 OHM 3 LHM 11 LHM + Nissen 21 dilation	186 156	1 perforation 2 perforations	Sutured Sutured	- -	75
Corda *et al*[24]	20	12 (5-15)	24	20 LHM	96 (60-160)	4 conversions OHM 5 dysphagia	 1 lap LOA 1 redo LHM 1 redo OHM	3 (1-5)	60
Esposito *et al*[26]	31	8.4 (5-15)	>12	31 LHM/Dor	120	3 perforations 5 dysphagia	2 sutured 1 redo HM 2 dilated 1 redo OHM	4 (3-8)	9-156
Tannuri *et al*[27]	15	12 (9-17)	30	15 LHM/Dor	90 (150-260)	2 dysphagia	1 botox injection	2.5 (1-4)	32.5 (2-96)
Patti *et al*[28]	13	15 (6-17)	24	13 LHM/Dor	144 ± 35	-	-	2	19
Lelli *et al*[29]	19	10 (1-17)	-	14 OHM 5 OHM + Belsey	-	2 dysphagia	2 dilation	8	108 (6-252)
Rothenberg *et al*[30]	9	12 (5-17)	6-24	4 THM 5 LHM/Dor	95 62	1 perforation 1 dysphagia 2 GERD 1 delayed perforation	Sutured Redo LHM Medical Rx Lap repair	2 1	-
Askegard-Giesmann *et al*[31]	26	15 (4-18)	-	1 LHM 2 LHM/Dor 23 LHM + Toupet	- 	1 perforation 1 perforation/aspiration 7 dysphagia 1 GERD	Sutured Sutured 3 redo LHM 3 dilation 1 botox Medical Rx	2.7 (1-4)	0-75 -20
Esposito *et al*[32]	8	6.3 (2-13)	> 121 LHM	6 LHM/Dor 2 LHM/Thal	120 (90-150)	3 perforations	3 sutured	4 (3-31)	6-60
Current Study	24	12.9 (5-18)	> 24	3 LHM 2 LHM/Thal 19 LHM/Dor	124 (45-213)	2 perforations 2 dysphagia	2 sutured 2 dilations 1 redo LHM	2.7 (1-6)	4 (4-24)

OHM: Open Heller myotomy; LHM: Laparoscopic Heller myotomy; THM: Thoracosopic Heller myotomy; Rx: Therapy.

the literature, there was 0%-26% recurrence rate of dysphagia after LHM with or without an anti-reflux procedure (Table 3)[16,24,26-30,33]. It is unclear if recurrent dysphagia is secondary to the nature of disease or failure of surgical treatment. Surgeon experience may contribute to decreasing rates of complications as suggested by Esposito *et al*[26] since their incidence of post-operative dysphagia dropped from 50%[33] to 16% with further experience. Our incidence of recurrent dysphagia is 8% compared to 11%, 16%, 25%, and 26%[29,25,26,31] in comparable sized series (19-31 patients). Perforation rates occur from 0%-15% (8% in ours) in larger series[16,24,29,31] but rarely require re-operation (Table 3). Accordingly, in smaller series and those from longer time periods in the past, perforation rates were higher (22%-50%) probably related to the establishment of a learning curve for the operation[30,33].

PER ORAL ENDOSCOPIC MYOTOMY

Peroral endoscopic myotomy (POEM) is a novel technique in the treatment of achalasia. POEM is one of few procedures utilizing natural orifice transluminal endoscopic surgery (NOTES) routinely in adults. POEM is an endoscopic procedure that directly treats the diseased tissue[23]. Pasricha *et al*[34] first described a submucosal endoscopic esophageal myotomy in animal studies for the treatment of achalasia. Inoue *et al*[35] coined the term peroral endoscopic myotomy and was the first to perform the procedure in 17 adult patients. Multiple studies have concluded that short-term outcomes of this procedure were safe[35-38].

Not all patients are suitable candidates for POEM. Contraindications include severe pulmonary disease, coagulation disorders, prior esophageal mucosal resection, or any prior therapy that has compromised the integrity of the esophageal mucosa[37]. POEM is performed utilizing flexible endoscopy, mucosal incision and dissection of a submucosal tunnel distally in the esophageal wall to approach the esophagogastric junction. A 2-3 cm longitudinal incision in the inner circular muscle approximately 4 cm from the LES, will produce similar results to

Heller myotomy[36,38]. A contrast esophagram is routinely obtained on the first postoperative day and the patient is started on a pureed diet if esophagram is normal[36-39].

Ren *et al*[40] reported 119 cases of achalasia treated with POEM, the most common postoperative complications included subcutaneous emphysema (55.5%), pneumothorax (25.2%), pneumomediastinum (29.4%), pleural effusion (48.7%), segmental atelectasis (49.6%), pleural effusion (48.7%), and pneumoperitoneum (39.5%). In this study, 13 patients with pneumothorax were treated with thoracic drainage and 2 patients with pleural effusion were treated with thoracentesis. The high incidence of pneumothorax, pneumomediastinum, subcutaneous emphysema, and pneumoperitoneum was attributed to the use of air insufflation during the procedure and subsequently this group now utilizes CO_2 insufflation[23]. Swanström *et al*[36] reported pneumoperitoneum in 3 out of 5 patients that were treated with Veress needle. Inoue and associates reported pneumomediastinum in multiple patients, however these patients did not require treatment although another patient in that series underwent thoracostomy drainage tube placement[39]. Feasibility of POEM is highly dependent on surgeon' s experience, duration of symptoms, prior pneumatic dilatations, and endoscopic therapies[41]. Nonetheless, multiple studies have reported POEM provides favorable outcomes and is relatively safe for the treatment of achalasia in adults[35-37,39-43]. Long-term outcomes (> 6 mo) for POEM in adult patients have been reported by Swanström *et al*[44] as significant in relieving dysphagia in 83%. Maselli *et al*[45] reported the first case of POEM performed in a 3-year-old with achalasia complicated by failure to thrive. At 1-year follow up, the patient was asymptomatic and had an appropriate weight for her age[45]. Familiari *et al*[46] reported 3 children treated with POEM for achalasia. There were no postoperative complications. In this study, 2 out of 3 patients had complete resolution of symptoms and the third patient had improvement in symptoms after 1-year follow up[46]. Although POEM is effective, minimally invasive, and safe in adults, there is also more recent evidence to suggest that the surgical approach (laparoscopic Heller myotomy) is more definitive and long lasting in relieving symptoms in these patients compared to endoscopic dilatation or botulinum toxin injection techniques[47]. It is apparent that effective therapy for children with achalasia is needed. Marlais *et al*[48] reported that children with achalasia have a significantly lower quality of life (QOL) compared to both children with inflammatory bowel disease and healthy children. While current evidence also suggests that the surgical approach provides lasting benefits for children with achalasia, future prospective evaluation will need to be conducted to ascertain whether POEM is safe and equally effective in children. For now, it is unclear; however pediatric surgeons are interested in learning this novel technique and employing its use in the management of pediatric achalasia.

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MINIREVIEWS

ESD training: A challenging path to excellence

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Abstract

Endoscopic submucosal dissection (ESD) has important advantages over endoscopic mucosal resection (EMR) for early gastrointestinal neoplasia treatment, but its difficult learning curve and associated risks have constrained its wider expansion. ESD training includes a comprehensive study of ESD basics, attending live cases and performing initial interventions in animal models, ideally under expert supervision. Mentoring methods in Japan and other Asian countries are reviewed, with a special concern in the conditions recommended for trainees to engage in an ESD program and achieve competence. Animal training is usually based on the well-known porcine model. *Ex vivo* models for esophageal, gastric and rectal ESD are cheap and easy to set up, whereas *in vivo* training requires special settings and veterinarian support. Nevertheless, it is advisable to gain experience in the live pig, with conditions that are similar to humans, before moving on to real patients. Particular attention is focused on colorectal ESD (CR-ESD), one of the most difficult locations for this technique. Since most of the potential lesions for ESD in Western countries are located in the colon or rectum, excellence in training is of paramount importance for successful outcomes in CR-ESD in the West.

Key words: Endoscopic submucosal dissection; Training; Early neoplasia; Animal model; Colorectal

Core tip: This mini review focuses on endoscopic submucosal dissection (ESD) training. ESD is a relatively novel advanced technique used for *en bloc* resection of gastrointestinal early neoplasia. ESD training has become a challenge for Western endoscopists due to several factors: low detection rate of early gastric cancer, the perfect scenario for starters; lack of experts in the technique for adequate tutoring; and finally, most of the target lesions in Western countries are colorectal neoplasias, representing the highest peak of difficulty in ESD. We will review some of the most important steps that could shape a training program in ESD, including animal training. Particular attention is focused on colorectal ESD.

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INTRODUCTION

The oncology field is already an important area of development for gastroenterologists[1] since diagnosis and/or treatment of early gastrointestinal neoplastic lesions is crucial for prevention and cure. Management of lesions with a low risk of lymph node metastasis usually comprises classic polypectomy and endoscopic submucosal resection (EMR). EMR has demonstrated good results dealing with esophageal, gastric, duodenal and colorectal lesions[2-5]. Ideal targets include flat lesions (Paris Classification 0-Ⅱa and 0-Ⅱb) less than 2 cm, although piecemeal resection is also possible with acceptable outcomes[2,6]. Endoscopic submucosal dissection (ESD) is a late step forward in therapeutic endoscopy for early gastrointestinal neoplasia[7] and has become a standard of care, not only in Japan where it originated in the late 1990s, but also in some

other countries and regions[8-17]. ESD has also spread in its indications: gastric, esophageal, colorectal, duodenal and even hypopharyngeal early neoplasia are potential targets, with excellent results[18]. New and exciting areas of research for ESD are now being explored, like the treatment of submucosal tumors[19,20] (Figure 1).

The main advantages of ESD compared to EMR are a higher *en bloc* and R0 resection rate[21-23], with decreased local recurrence, no limitation due to size of the lesion in certain circumstances and superior pathological assessment of the cancer invasion in the specimen[24,25]. Nevertheless, ESD is associated with a higher risk of severe complications (bleeding and perforation) (Figure 2), in addition to a particularly difficult and long learning curve[21,26-28]. The latter, together with the lack of experts available for tutoring, are the most important restricting factors for a wider expansion of ESD in Western countries[11]. The lower gastric cancer incidence, with a lower proportion of early gastric cancer diagnosed during upper endoscopy procedures, also contributes to the low penetration of ESD in Western areas[13,29]. Those are the ideal cases for initial training in human ESD, as recommended by experts[9,18,30]. Unfortunately, this painful scenario for training is aggravated by the fact that many potential lesions for Western endoscopists to perform ESD are mostly found in the colon and rectum, a particularly challenging location, even for Japanese experts[31,32]. Some of the most important aspects of ESD training, with a particular section focused on colorectal ESD (CR-ESD), will be reviewed.

JAPANESE EXPOSURE: THE ORIGINAL SOURCE

ESD was initially developed in Japan and Japanese experts have propelled this technique to its highest standards and excellent outcomes[33,34]. In Japan, the usual way of teaching new apprentices in ESD has traditionally consisted of supervised ESD procedures by senior endoscopists in referral centers (Figure 3). This scheme seems to have worked well in recent years, but as the number of physicians performing ESD and its indications are rising, it seems that even in Japan some kind of standardized ESD training program for teaching centers is needed[35]. Most of the candidates should have demonstrated advanced skills in therapeutic upper and lower endoscopy, as well as extensive knowledge of early neoplasia endoscopic assessment. Moreover, many mentors do consider aptitudes like perseverance, competence in dealing with stressful situations and awareness of own limitations on their mentee selection process.

Gastric ESD is contemplated as the first step in the ESD career since the easier position and thick wall facilitates the ESD approach with a lower risk of perforation. Screening programs in gastric cancer have boosted the detection and knowledge of early gastric cancer in Japan[36]. Basic competence in terms of *en bloc* resection and complication rate can be reached after 30 human gastric

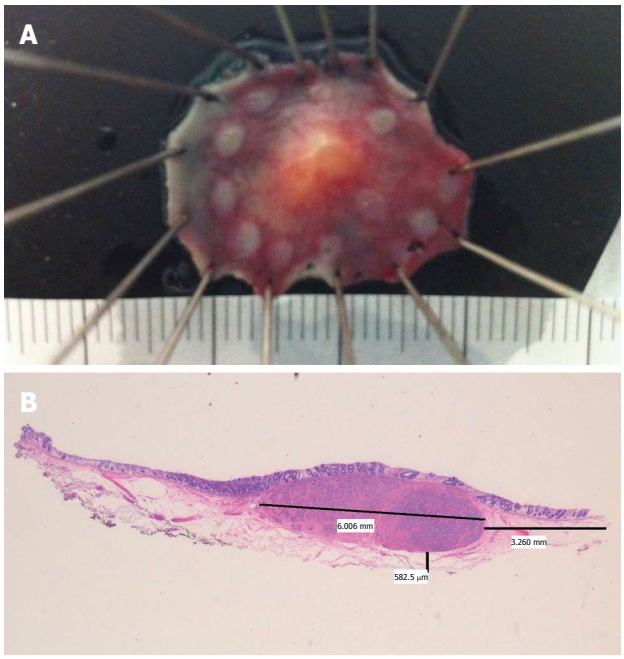

Figure 1 Rectal neuroendocrine tumor. A: Specimen fixed after successful endoscopic submucosal dissection; B: Hematoxylin and eosin × 10. Neuroendocrine tumor, 6 mm largest diameter. Free lateral and depth margins (R0) (courtesy of Dr. Isabel Salas, Puerta de Hierro University Hospital).

cases have been completed under expert supervision[28,37]. Tsuji *et al* have described excellent results for trainees who completed 27-30 gastric ESD after having attended 40 cases and later completing 20 cases of post-ESD preventive coagulation[38]. A recent study suggests that expertise similar to well-experienced endoscopists could be achieved after having completed 80 cases, including lesions within extended criteria (ulceration, large size *etc.*)[39]. Some suggested the criteria for skill advances monitoring as speed, size and *en bloc* resection rate[28], but the location in the stomach is also a decisive factor, with more difficult cases in the body and fundus[10,39].

For many foreign physicians with an interest in ESD, Japanese teaching centers are a good opportunity for first-hand exposure in its "natural" environment[40]. They can experience how the experts perform high quality diagnostic evaluation of target lesions and perform ESD. Essential knowledge to acquire includes, but is not limited to, dye and digital chromoendoscopy, magnification endoscopy, marking and initial approach to lesions, step by step ESD procedure, tools and devices, management of minor and major complications, post-ESD surveillance and specimen fixation and pathological assessment. Overseas endoscopists are not usually allowed to do hands-on training in humans in Japan, yet they can still practice ESD in animal models with the unique opportunity of onsite expert supervision[41] (Figure 4). Furthermore, it is possible to invite Japanese experts to Western centers to get tutoring support for an initial ESD approach[42,43] (Figure 5).

In recent years, relevant progress in ESD has been observed in other neighboring countries in southeast

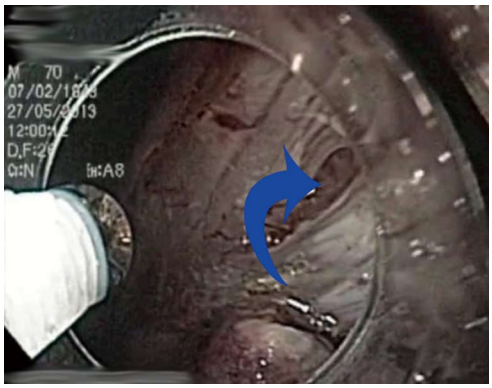

Figure 2 Small perforation (blue arrow) in the anterior wall of the stomach after endoscopic submucosal dissection of intramucosal adenocarcinoma (T1a, R0).

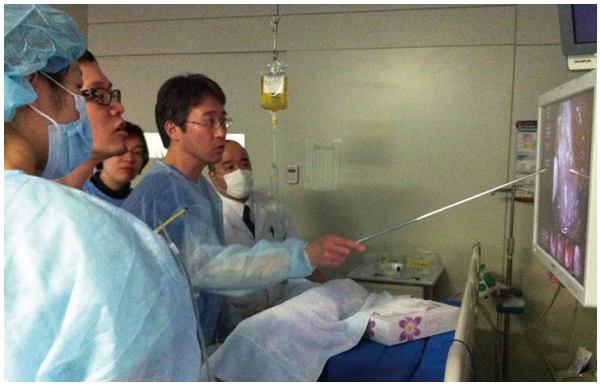

Figure 3 Professor Toyonaga supervising human endoscopic submucosal dissection case performed by young trainee. Kobe University Hospital, Japan.

Figure 4 Dr. Morita supervising live animal endoscopic submucosal dissection case performed by trainee (Dr. Herreros de Tejada). 2nd KOBE International endoscopic submucosal dissection and EUS-FNA Hands-on-Seminar Kobe University Hospital, Japan.

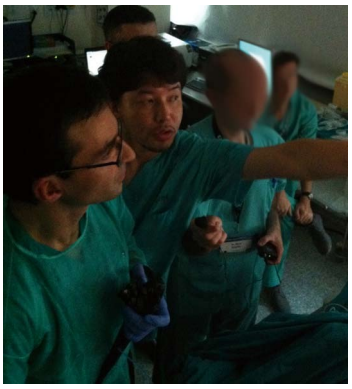

Figure 5 Dr. Morita supervising human rectal endoscopic submucosal dissection case performed by trainee (Dr. Herreros de Tejada). International endoscopic submucosal dissection Live Madrid 2013 Clinical and Hands-on Course. Puerta de Hierro University Hospital, Madrid, Spain.

Asia, mainly in South Korea[10,44] and China[45]. In South Korea, eligible trainees with a 2-year experience in endoscopy must observe 30-40 ESD cases to follow all steps of the procedure, including fixation of the specimen once completed; afterwards, they would serve as an assistant with knives to an expert endoscopist for 15-20 cases before being allowed to start ESD with small lesions in the antrum under close supervision[46]. As an additional reinforcement, the national Korean ESD group conducts an *ex vivo* hands-on course for trainees[30,47]. In the near future, we can expect high quality expert groups in Korea also offering additional opportunities for ESD training to overseas trainees.

ANIMAL TRAINING: THE WILD EXPERIENCE

Training in animal models is probably the best way to overcome some of the limitations in learning ESD[41,48]. Such a difficult technique must not be attempted in humans unless supervised by certified experts, or after an intensive animal training program has been completed and satisfactory outcomes have been achieved. The porcine model is similar to human anatomy, not expensive and widely accessible[46]. Reports of ESD in other species are scarce[16,49], including a description of a human excised portion from a sleeve gastrectomy[50]. Most studies have demonstrated the usefulness of the porcine *ex vivo* and *in vivo* for initial competence achievement in ESD, where regular endoscopes can be used and anatomic similarities in esophagus and stomach facilitates the approach[43,45,48,51,52]. The trainee can experience the early steps of the ESD process (marking, circumferential cutting and submucosal dissection), together with management of complications such as perforation and bleeding (only *in vivo* model). Some suggested the criteria for skill advances monitoring are speed and *en bloc* resection rate[53,54]. An animal training program in ESD requires appropriate settings and dedicated endoscopy equipment and materials (Figure 6), all of which is not commonly accessible to many trainees in their institutions. Some endoscopists attend special courses in ESD to get access to animal training, with good results in terms of skill improvement[43,45].

Ex vivo model

Harvested porcine organs like esophagus and stomach

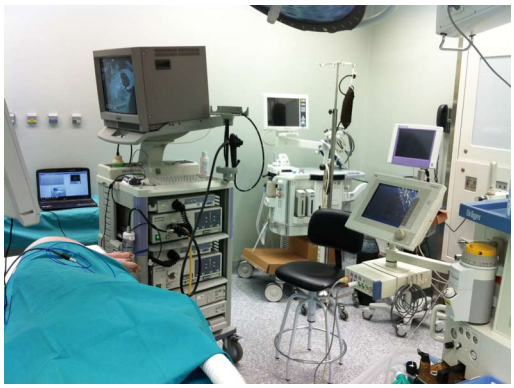

Figure 6 Operating room with equipment ready for endoscopic submucosal dissection. Animal Research Lab. IDIPHIM. Puerta de Hierro University Hospital, Madrid, Spain.

Figure 7 Freshly harvested porcine stomach (A) and rectum (B) attached inside a plastic box for *ex vivo* model. Animal Research Lab. IDIPHIM. Puerta de Hierro University Hospital, Madrid, Spain.

are easy to set, cheap and there is no need for veterinarians or anesthesia[37,40,46]. It is not acceptable to start in the live animal before being familiarized with maneuvers and the initial steps of ESD. Perforation and associated mortality are common in live animals for those novices with no experience[45]. The freshly harvested organ should be intensively cleaned before attaching the proximal esophagus to an insertion tube inside a plastic box or placing the organ in a plastic model. A similar setting has been described for porcine harvested rectum (Figure 7), with good results for CR-ESD[55]. Although these models do not reproduce real *in vivo* conditions, like spontaneous motility, bleeding and tissue reaction to injection and electrocautery, the trainee can practice special maneuvers, injection, circumferential cutting and dissection. This initial phase is a good opportunity to be familiarized with different knives and devices. Insulated knives are recommended for the naïve trainee, since non-insulated knives may be associated with a higher perforation risk[45]. It is recommended that the novice should get acceptable *en bloc* resection and perforation-free results before stepping up to live animals[48]. The general recommendation for the trainee is to initiate ESD in porcine stomach, starting in the antrum, and then progressing according to an increasingly difficult gradation to the body, the greater curvature, the lesser curvature and the fundus[43]. Afterwards, the trainee might practice in more demanding locations like the esophagus or rectum, for which a specific *ex vivo* model preparation has been described elsewhere[51,55].

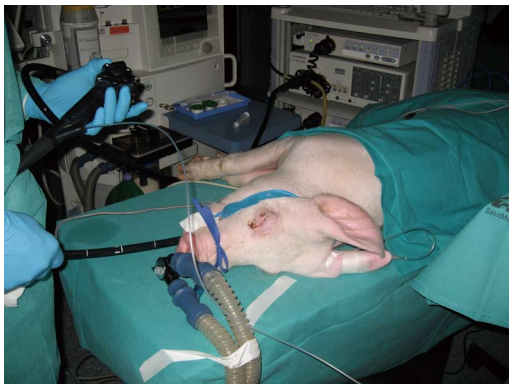

Figure 8 Gastric endoscopic submucosal dissection performed in live pig under general anesthesia. Animal Research Lab. IDIPHIM. Puerta de Hierro University Hospital, Madrid, Spain.

In vivo model

The *in vivo* model is the natural and ethically accepted next step after a sufficient period of training in the *ex vivo* model. Using live pigs requires support from veterinarians to provide preparation of the animal (24-48 h fasting is advisable), general anesthesia and euthanasia/follow-up care of the animal after procedures are completed (Figure 8). The sense of reality increases when performing ESD in live animals, with physiological reactions, including motility, mucosal secretions, bleeding and abdominal distension. In survival studies, perforation closure outcomes and post-ESD scars can be checked, which gives a chance for practicing ESD in difficult scenarios (severe fibrosis, ulceration) afterwards. This simulation can also be set up in *ex-vivo* models using banding and snare transection[56], but a more realistic approach seems to be the live animal. Once the trainee has gained enough experience in the stomach, he/she could move forward to the esophagus or the rectum and colon. Whereas the former requires a similar setting to the stomach, the rectum and colon demand an intensive preparation with bowel cleaning agents and frequently additional water infusion of the rectum[40](Figure 9).

IMPROVING YOUR SKILLS: WISE ADVICE FROM EXPERTS

There is some general advice for endoscopists already performing ESD in humans that should be kept in mind. A good field of vision and situation of the scope in relationship to the target lesion are of paramount importance. The endoscopist must know how to change the patient´s position to get the best of gravitational counter traction and a clear view to facilitate the access to the submucosal layer[57]. Managing the retroflex position ac-

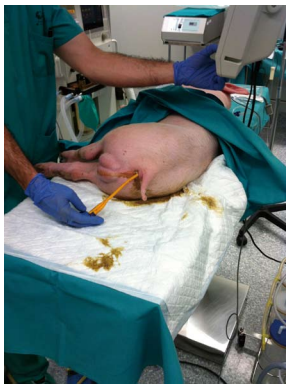

Figure 9 Preparation for rectal endoscopic submucosal dissection with intensive rectal water infusion of the rectum. Animal Research Lab. IDIPHIM. Puerta de Hierro University Hospital, Madrid, Spain.

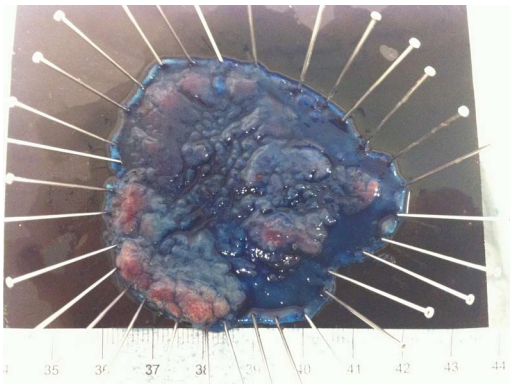

Figure 10 Colorectal-endoscopic submucosal dissection specimen fixed: LST Granular mixed type, 60 mm longest diameter located in descending colon. Puerta de Hierro University Hospital, Madrid, Spain.

curately is particularly important when performing gastric ESD, where the fundus and body locations usually require such an approach. Getting used to dissecting while positioning in such an "inverted" fashion will demand hours of hard training, ideally in the animal model setting. It has been suggested that the appropriate level for dissection is for the depth to be beneath the vascular network and above the muscle layer, so to reduce bleeding events during ESD, as well as the risk of positive vertical margin[58]. A similar recommendation is also true for lesions with severe fibrosis and, if possible, we should try to create a nice flap starting far from the lesion border. Good quality of field of vision is paramount and experienced endoscopists recommend performing a careful and systematic hemostasis of bleeding points or, even better, appropriate preventive hemostasis of visible vessels[59]. Special care should be given to the systematic coagulation of all visible vessels in the resection site after completing the resection[58]. Animal training has been essential for introducing ESD practice in Western countries[40,42], but it also plays an important role for those endoscopists engaged in human ESD who still need to increase their skills to be able to face difficult ESD locations (colon, gastric fundus *etc.*). Another aspect we should bear in mind is the great importance of preserving a complete and systematic registry of all ESD cases, so that short and long term outcomes/adverse events in our series can be analyzed[11].

COLORECTAL ESD (CR-ESD): THE HIGHEST PEAK

Although gastric ESD became a standard procedure in Japan and other Asian countries a long time ago, CR-ESD is still a challenging procedure, even for Japanese experts. Most of the experience in CR-ESD comes from large studies in Japan[34,60-62]. Eligible flat colorectal lesions for ESD are increasingly diagnosed in Japan and Western countries[63-65] and will rise even more in the near future with the expansion of colorectal screening[66,67]. Absolute indications for ESD in Japan include LST-NG > 20 mm, LST-G mixed type > 40 mm and any lesion with severe fibrosis (due to EMR, biopsies or inflammatory bowel disease)[34,60,68] (Figure 10). There is controversy regarding the adoption of CR-ESD due to the high risk of failure and complications and, since EMR appears to be good enough for the management of colorectal sessile non-invasive neoplasia[2], there are advocates for exploring alternative hybrid techniques with ESD steps associated with EMR[69].

The learning curve for CR-ESD has been analyzed in several studies. Apparently, up to 80 cases might be needed to be completed before getting excellent results (*en bloc* and R0 resection)[70]. Sakamoto *et al*[71] reported a progressive learning curve by 2 supervised trainees, reaching competence level after 30 CR-ESD. Other authors have recommended a caseload of 20 or 30 gastric ESDs before attempting CR-ESD[60,72]. It is possible that this learning curve could be reduced if additional training is completed in the animal model while performing the first human cases in the rectum, where maneuverability is easier and perforation has less impact on the patient[32]. In the learning process of CR-ESD, it might be acceptable to approach smaller lesions in the rectal location (relative indication for ESD) in order to gain experience and avoid despair[27,32].

A recent European position statement in ESD recommended steps that should be taken to acquire good skills in CR-ESD: following a progressive training, mainly in animal models, and keeping a track record[11]. There are some series of CR-ESD in European centers which show inferior outcomes, slower progression and a limitation of distal locations compared to Japanese counterparts[27,73,74]. Still, results are encouraging and a recent report showed acceptable R0 and *en bloc* resection rates in the rectum and colon after 5 and 20 cases respectively[42]. Some Japanese experts reassure us that inexperienced Western endoscopists should not try CR-ESD in lesions with significant fibrosis or larger than 40 mm during the first 30-40 cases[32].

Selected tips for CR-ESD

Adequate positioning and a high risk of perforation are the main limitations when trying to perform successful CR-ESD. You will learn from each of your cases and you should be prepared to face complications calmly to manage them and move forward. Here is some general advice for starters from my limited personal experience: (1) Ask for proper advice from experts when planning CR-ESD. It might be very useful to send pictures and/or video clips of the lesion beforehand to an expert so that you can get recommendations of whether it is eligible for ESD, suitable or not for your level of experience, tips for the approach *etc.*; (2) Consider general anesthesia for CR-ESD. You may spend many hours when approaching difficult locations and regular soft breathing moves can help you get the scope stabilized and avoid unexpected bowel movements than could facilitate an unintentional perforation. Extended deep sedation with regular drugs (propofol, midazolam, pethidine *etc.*) might induce the patient to experience intense snoring, resulting in bowel "bouncing" that makes ESD hard enough; (3) Have some rest. When performing ESD, any minor mistake can waste all your work, so it is essential to be fresh and alert. This is not easy after some hours of tense concentration, especially in the initial period of training when CR-ESD takes so long. You should consider a break after 75-90 min of a procedure when the time of reaction and concentration level may start to decline; and (4) Do record all your procedures so you are able to review your mistakes. It is especially useful to watch those moments prior to unintentional perforation so you can learn what not to do next time. Most of the time, it is a question of an excessive push of the knife or an approach in the wrong direction.

CONCLUSION

ESD is an advanced technique for early neoplasia treatment in continuous expansion, with important advantages over EMR. However, the difficult learning curve is still the main restricting factor. Training in ESD is a long and hard journey that will require comprehensive study of the ESD essentials, attending live cases, completing an animal training program using both *ex vivo* and *in vivo* models, and finally moving on to human cases under an expert´s close supervision. For Western endoscopists, this journey will be particularly arduous, with CR-ESD as the foremost challenge. And yet, most potential candidates for ESD are and probably will be colorectal early neoplasias. Intensive preparation with all available means of training is key for actual and future trainees initiating ESD. As quoted by Prof. Toyonaga, "…ESD can be a superb treatment method that is extremely beneficial for patients when the quality is well secured…"[58]. In other words, ESD in an excellent technique and there is no substitute for excellence in ESD training.

"*Never, never, never give up*" - Winston Churchill.

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MINIREVIEWS

Current status and future applications of contrast-enhanced endoscopic ultrasonography

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Abstract

Endoscopic ultrasonography (EUS) is currently an integral investigation of many gastrointestinal disorders. It has been shown to have a higher efficacy than conventional computed tomography in detection and characterization of small lesions especially in the pancreas. Much effort has been put to further improve the sensitivity, specificity and overall accuracy of EUS. One of the major advances is the utilization of contrast agents for better delineation of the vascularity and tissue perfusion of the target lesion. This article describes the basic principles of ultrasound contrast agents and the different modalities used in contrast-enhanced EUS (CE-EUS) including contrast-enhanced Doppler EUS (CED-EUS) and contrast-enhanced harmonic EUS (CEH-EUS). In addition, the current applications of contrast enhanced EUS in different gastrointestinal conditions were discussed. Furthermore, the future development of hybrid approaches combining CE-EUS with other imaging modalities and the potential therapeutic aspect of using it as a vector for drug delivery were also discussed.

Key words: Endoscopic ultrasonography; Contrast-enhanced endoscopic ultrasonography; Advanced endoscopic ultrasonographic imaging

Core tip: This article provides a focused update on the current applications of contrast enhanced endoscopic ultrasonography in the gastrointestinal tract. Recent advances and future developments in contrast enhanced EUS are discussed.

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INTRODUCTION

Endoscopic ultrasonography (EUS) is currently an integral investigation of many gastrointestinal disorders. It has been shown to have a higher efficacy than conventional computed tomography in detection and characterization of small lesions especially in the pancreas[1]. Much effort has been put to further improve the sensitivity, specificity and overall accuracy of EUS. One of the major advances is the utilization of contrast agents for better delineation of the vascularity and tissue perfusion of the target lesion. This article aims to review the current status of contrast enhanced EUS and to provide insights into future applications of the technology in the gastrointestinal tract.

ULTRASOUND CONTRAST AGENTS

Contrast agents used in EUS are gas-containing microbubbles encapsulated in a resistant shell[2]. This shell decreases dissolution or disruption of the microbubbles in the blood stream. When hit by an ultrasonic wave, the microbubbles would oscillate and generate an acoustic signal that would be detected and reproduced on an ultrasound image[3,4]. At a low acoustic power, a nonlinear return signal containing multiples of the resonating frequency would be detected[5]. These higher frequency components, known as harmonics, are fundamental to the "enhancement" detected when performing contrast-enhanced harmonic ultrasonography[6].

Three generations of ultrasound contrast agents have been developed based on their capability of transpulmonary passage and half-life in the human body (Table 1)[7]. First generation agents are microbubbles filled with air, but they generally require high acoustic power to produce oscillation or break its microbubbles. Second generation agents, including the commonly used SonoVue™ and Sonazoid™, are composed of gases that are less soluble and less likely to leak out from microbubbles, thereby lasting longer in the circulation. These agents can be oscillated or broken by lower acoustic power, and thus are more suitable for EUS because of the limited acoustic power produced by the small transducer. Third generation agents (Echogen™) are capable of phase shifting from liquid to gas form once they reach body temperature. These agents are not widely used in EUS of the gastrointestinal tract as yet. Ultrasound contrast agents are generally safe, and adverse reactions are rarely observed. The macromolecules within the agent could lead to allergic reactions, which mostly are mild. There is also minimal clinical significance regarding the toxic or embolic potential and biological effects of these ultrasound contrast agents[5].

Table 1 Contrast agents for ultrasonography[7]

Contrast agent	Composition	Manufacturer
First generation		
Albunex	5% Sonicated serum albumin with stabilized microbubbles	Mallinckrodt
Echovist (SHU 454)	Standardized microbubbles with galactose shell	Schering
Levovist (SHU 508)	Stabilized, standardized microbubbles with galactose, 0.1% palmitic acid shell	Schering
Myomap	Albumin shell	Quadrant
Qantison	Albumin shell	Quadrant
Sonavist	Cyanoacrylate shell	Schering
Second generation		
Definity/ luminity	C3F8 with lipid stabilizer shell	Bristol-Myers Squibb Medical Imaging
Sonazoid	C4F10 with lipid stabilizer shell	GE Healthcare
Imagent-Imavist	C6F14 with lipid stabilizer shell	Alliance
Optison	C3F8 with denatured human albumin shell	GE Healthcare
Bisphere/ carbiosphere	Polylactide-coglycolide shell with albumin overcoat	Commercially unavailable
SonoVue	SF6 gas with lipid stabilizer shell	Bracco
AI700/imagify	C4F10 gas core stabilized with polymer shell	Acusphere
Third generation		
Echogen	Dodecafluoropentane (DDFP) liquid in phase shift colloid emulsion	Sonus Pharmaceuticals

CATEGORIES OF CONTRAST ENHANCED ENDOSCOPIC ULTRASONOGRAPHY

After intravenous contrast injection, sonographic assessment of the target of interest could be performed by two methods: contrast enhanced color/power Doppler imaging (CED-EUS) and contrast enhanced harmonic imaging (CEH-EUS). Contrast injection in conventional B-mode ultrasound is not recommended as it would not improve imaging quality and the detection of contrast agents is poor in the presence of surrounding tissue. When contrast agents are used with Doppler EUS, it would allow detection of intratumoral vessels with enhancement of tumor vascularity[8-14]. However, vessels with slow flow are still poorly depicted, as this mode has a low sensitivity to low blood flow[6,9,15]. Blood flow from surrounding vessels can also create motion and blooming artifacts, increasing the difficulty in evaluation of tumor vascularity. Motion artifacts refer to low signal intensity of flowing blood when compared to that of tissue movement, while blooming artifacts refer to the widened appearance of a blood vessel with power Doppler[6].

CEH-EUS was recently developed to overcome the difficulties experienced with Doppler EUS. As mentioned above, the harmonic component refers to the return signal of multiples of the fundamental frequency. The harmonic component derived from microbubbles is higher than that from tissues, and the harmonic imaging technique detects these signals. It also filters signals that originate from the tissue by selectively detecting the harmonic components, thereby producing images that depict vessels with very slow flow without Doppler related artifacts[6].

Dietrich *et al*[16] first reported the use of CEH-EUS in 2005. In their study, they demonstrated the possibility of arterial, portal venous and parenchymal contrast enhancement after injection of a second generation contrast agent. Kitano *et al*[17,18] also reported their initial experience with a novel echoendoscope (XGF-UCT260W; Olympus Medical Systems Co. Ltd., Tokyo, Japan) that was equipped with a broadband transducer and extended pure harmonic detection mode. Pancreatic parenchymal perfusion and branching vessels were only observed after contrast injection with the harmonic mode but not the power-Doppler mode, enabling further improvement in accuracy of assessment of tissue vasculature (Figure 1). Since then, numerous studies have reported the use of this novel technique for assessment of different gastro-

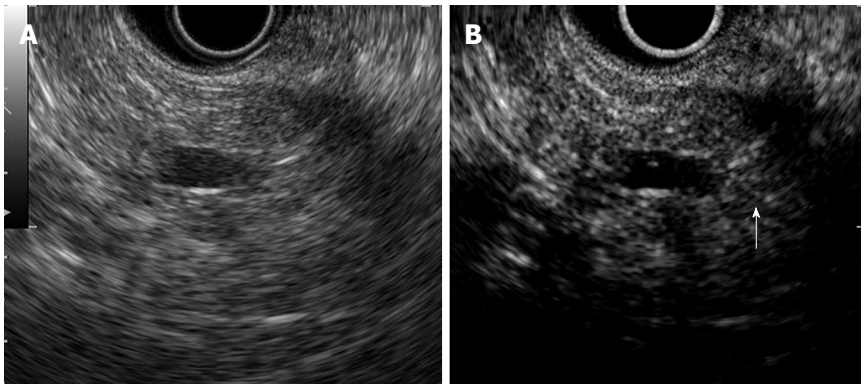

Figure 1 Contrast-enhanced harmonic-endoscopic ultrasonography images of pancreatic parenchymal perfusion. A: Conventional B-mode image; B: Contrast-enhanced harmonic image. Arrowhead indicates pancreatic parenchyme with small vasculature.

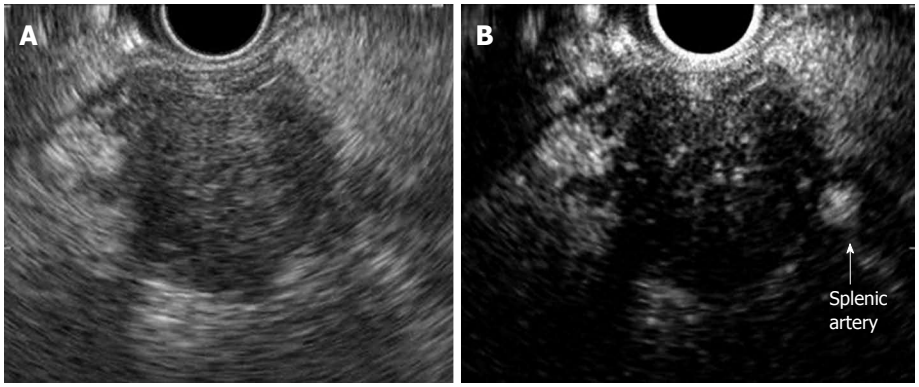

Figure 2 Hypoenhancing pancreatic tumour. A: Conventional B-mode image; B: Contrast-enhanced harmonic image.

intestinal and pancreatic pathologies. However, inter-observer agreement of CEH-EUS was only found to be fair to moderate[19]. Upon a review of 80 EUS videos by 15 endosonographers, overall inter-observer agreement was moderate for the uptake of contrast agents (k = 0.567) and fair for the pattern of distribution (k = 0.304) and the washout velocity (k = 0.369). This finding highlighted a major limitation of the technique that qualitative image analysis of contrast enhanced images is subjected to individual interpretation.

CURRENT APPLICATIONS OF CONTRAST-ENHANCED EUS

Pancreatic solid lesions

Differentiation between pancreatic ductal carcinoma and other pancreatic pathologies such as autoimmune pancreatitis and neuroendocrine tumors is difficult by conventional EUS. By CEH-EUS, four types of enhancement patterns have been reported previously: non-enhancement, hypo-enhancement, iso-enhancement and hyper-enhancement[20]. Hypo-enhancement pattern has been identified as the most common distinguishing feature of pancreatic adenocarcinoma (Figure 2). A recent meta-analysis including studies of both contrast enhanced Doppler EUS and contrast enhanced harmonic EUS reported an overall high sensitivity of 94% (95%CI: 0.91-0.95) and specificity of 89% (95%CI: 0.85-0.92) in diagnosing pancreatic adenocarcinoma[21-26]. Kitano *et al*[20] reported the largest series of 277 patients with solid pancreatic lesions who underwent contrast enhanced harmonic EUS with Sonazoid™. When compared with multi-detector contrast enhanced computed tomography, CEH-EUS yielded a significantly higher accuracy in diagnosing pancreatic adenocarcinomas that were less than 2 cm in size, with a sensitivity of 91.2% (95%CI: 82.5-95.1) and specificity of 94.4% (95%CI: 86.2-98.1). Furthermore, CEH-EUS was also superior in predicting the T-stage of pancreatobiliary tumors as compared with conventional EUS. In particular by CEH-EUS, the wall of the portal vein was better depicted, enabling better visualization of portal vein invasion and providing valuable information for surgical planning for vascular resection[27]. In patients with unresectable carcinoma of the pancreas, CEH-EUS has also been demonstrated to aid in predicting efficacy of chemotherapy. The presence of intratumoral vessels predicted a better progression free and overall survival after chemotherapy[28].

On the other hand, a hyper-enhancing pattern was identified to be a common feature in pancreatic neuroendocrine tumors (PNETs), with a sensitivity of 78.9% and a specificity of 98.0%[20] (Figure 3). The presence of filling defects within an enhancing pancreatic lesion cor-

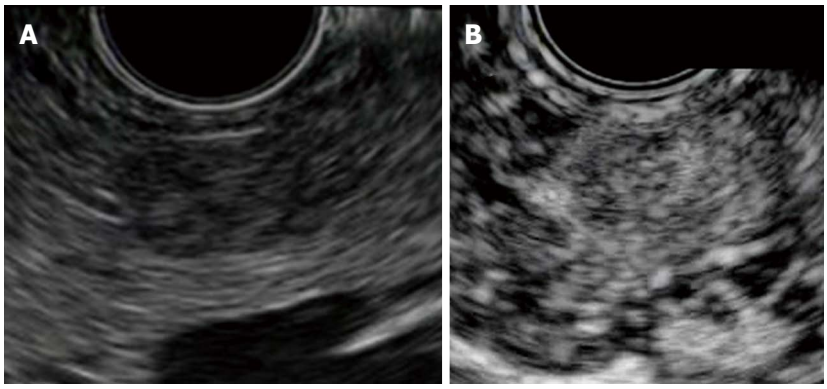

Figure 3 Hyperenhancing pancreatic insulinoma. A: Conventional B-mode image; B: Contrast-enhanced harmonic image.

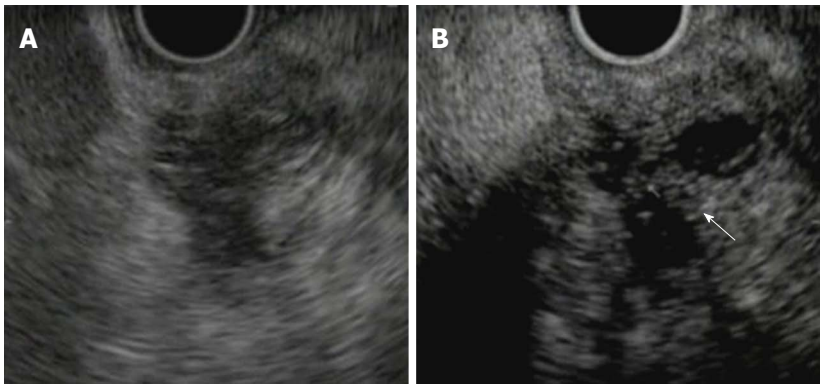

Figure 4 Contrast enhancing mural nodules of a pancreatic cystic neoplasm. A: Conventional B-mode image. B: Contrast-enhanced harmonic image. Arrow indicates mural nodule.

responded to hemorrhage or necrosis of malignant diseases as seen on pathological examination. This may have a potential role in differentiating benign versus malignant PNETs[13].

Pancreatic cystic lesions

The differentiation between benign and malignant intraductal papillary mucinous neoplasms (IPMNs) of the pancreas is difficult. Mural nodules have been identified as one of the most important indicator in the prediction of malignancy. A study published in 2009 demonstrated the ability of contrast enhanced EUS in characterizing mural nodules found in IPMNs[29] (Figure 4). Mural nodules were classified into four types based on the CE-EUS findings, and types Ⅲ (papillary nodule) and Ⅳ (invasive nodule) patterns were more frequently associated with invasive cancer, at 88.9% and 91.7%, respectively. A subsequent series by the same group of authors also found that only CE-EUS identified the presence of mural nodules in 27.3% of cases with proven malignant IPMNs after surgical resection[30]. Accurate differentiation between true mural nodules from mucous clots could also be achieved by contrast enhanced EUS[31].

Gastrointestinal stromal tumors

In a study of 17 patients with gastro-esophageal submucosal lesions, CEH-EUS was able to differentiate between gastrointestinal stromal tumors (GISTs) and other benign submucosal tumors such as leimyoma or lipoma by the pattern of contrast enhancement[32]. All 9 histologically proven GISTs showed hyperenhancement after contrast injection.

CEH-EUS has also been utilized to differentiate between low grade versus high grade malignant GISTs. In a study by Sakamoto *et al*[33], two distinctive vascular patterns were identified by CEH-EUS. Type Ⅱ pattern demonstrating irregular vessels on vessel image and heterogeneous enhancement on perfusion image was more commonly found in high grade malignant GISTs (Figure 5). The overall sensitivity, specificity and accuracy in prediction of malignant risk were 100%, 63% and 83%, respectively. A significantly higher sensitivity of CEH-EUS in detecting intra-tumoral vessels among high-grade malignant GISTs was also demonstrated when compared with multidetector computed tomography (CT) and power-Doppler EUS.

Gallbladder and bile duct lesions

The utilization of CEH-EUS in differentiating cholesterol polyps, gallbladder adenoma and gallbladder carcinoma has been studied. The sensitivity and specificity of CEH-EUS for differential diagnosis of gallbladder adenoma and cholesterol polyps based on the enhancement pattern were 75.0% and 66.6%, respectively, according to a study

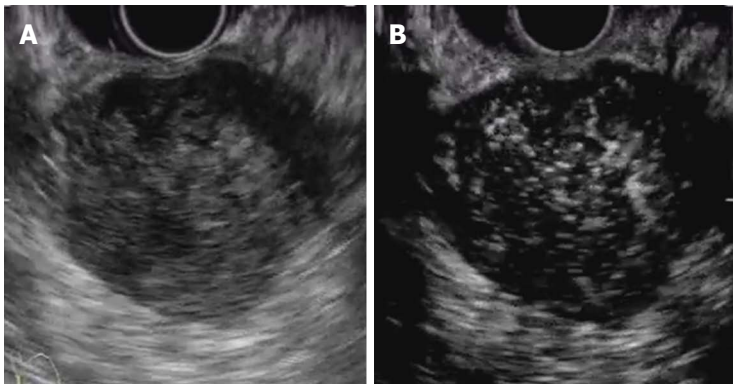

Figure 5 Heterogeneous enhancement with perfusion defects present in high grade gastrointestinal stromal tumors. A: Conventional B-mode image; B: Contrast-enhanced harmonic image.

by Park *et al*[34]. In another study of 93 gallbladder polyps > 1 mm, identification of irregular intratumoral vessels and perfusion defect aided in diagnosing malignant from benign gallbladder polyps, with a sensitivity of 93.5% and a specificity of 93.2%[35].

Bile duct thickening is a common feature in both benign and malignant biliary conditions such as primary or secondary sclerosing cholangitis and bile duct carcinoma. Studies have shown that contrast enhancement in the bile duct wall corresponds to non-neoplastic changes of the bile duct as in cholangitis[36,37].

Intra-abdominal lesions of undetermined origin

Contrast enhanced EUS has been found to be useful in differentiating benign versus malignant intra-abdominal lesions of unknown origin. In a study published by Xia *et al*[38], 43 patients with such a condition underwent CEH-EUS. Correlating with FNA results, the differentiation of malignancy was made by identifying heterogeneous enhancement within these lesions, with a sensitivity, specificity and accuracy of 96.3%, 100% and 97.6%, respectively. Of note, most lesions in the series were indeed intra-abdominal lymphadenopathies with benign or malignant changes.

Visceral vascular assessment

In a small study of 12 patients, all visceral vascular lesions were accurately diagnosed by the use of combined Doppler and CEH-EUS, including one undefined lesion by abdominal CT. The findings of EUS helped determine the appropriate intervention without radiation exposure[39].

Contrast enhanced EUS has also been utilized in other upper gastrointestinal diseases, including the depth of invasion in gastric carcinoma[40] and hemodynamic assessment of esophageal varices[41,42].

FUTURE DEVELOPMENT OF CONTRAST ENHANCED ENDOSCOPIC ULTRASONOGRAPHY

As stated previously, contrast enhanced EUS has been criticized for its qualitative nature. Quantitative methods have been proposed to improve the reliability. Two groups of authors reported the results with time intensity curve (TIC) of contrast uptake in differentiating pancreatic diseases[43,44]. According to Matsubara and colleagues, pancreatic carcinoma, in contrast to other pancreatic pathologies, yielded the greatest echogenic intensity reduction rate from the peak at 1 min after contrast injection. The diagnostic accuracy of EUS in combination with TIC reached 94.7% in their study[44].

A hybrid approach combining EUS with other imaging modalities has also been investigated recently. It was based on electromagnetic position tracking of the EUS transducer position and co-registration with a planar reconstructed image from those obtained on CT or magnetic resonance imaging[45,46]. A preliminary study has demonstrated that estimation of tumor angiogenesis through combining different imaging modalities was possible[47]. It may also increase the diagnostic accuracy through direct comparison of the target lesion by different imaging techniques. Furthermore, improved selection and enhanced visualization are possible for EUS guided FNA of lesions that are not clearly visible in the EUS field[48]. Contrast enhanced EUS could also help determine the likelihood of a false negative FNA result for pancreatic solid lesions.

The therapeutic potential of contrast enhanced ultrasonography has also been explored. Drug substances, such as plasmid DNA, could be delivered within the microbubbles of ultrasound contrast agents. Upon exposure to ultrasonic waves with very high acoustic power, rapid disintegration of microbubbles would occur and the drug within the microbubbles could be released. When combined with endoscopic ultrasound, the technique may aid in targeted drug delivery in pancreatic tumors[5,49,50].

CONCLUSION

With the recent advances in contrast enhanced EUS and CEH-EUS, better characterization of different gastrointestinal pathologies could be achieved. Furthermore, contrast enhanced EUS could play an increasingly important role in diagnosis and management of these conditions in

the future.

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ORIGINAL ARTICLE

Accuracy of transnasal endoscopy with a disposable esophagoscope compared to conventional endoscopy

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Abstract

AIM: To assess feasibility of unsedated esophagoscopy using a small-caliber disposable transnasal esophagoscopy and to compare its accuracy with standard endoscopy.

METHODS: We prospectively included subjects who were referred for upper endoscopy. All subjects underwent transnasal endoscopy with E.G. Scan™. The disposable probe has a 3.6 mm gauge and at its distal end there is a 6 mm optical capsule, with a viewing angle of 125°. Patients underwent conventional endoscopy after the completion of E.G. Scan™. We describe the findings detected by the E.G. Scan™ and calculate the diagnostic accuracy, sensitivity, specificity, positive predictive value, negative predictive value and Kappa index for esophageal diagnosis.

RESULTS: A total of 96 patients (54 women), mean age of 50.12 years (14 to 79), were evaluated. In all cases we were able to perform esophagoscopy with E.G. Scan™. The average realization time was 5 min. A total of 58 alterations were detected in the esophagus, 49 gastric abnormalities and 13 duodenal abnormalities. We found that for esophageal varices, E.G. Scan™ has sensitivity, specificity and diagnostic accuracy of 95%, 97% and 97%, respectively. Kappa coefficients were 0.32 for hiatal hernia, 0.409 for erosive gastroesophageal reflux disease, 0.617 for Barrett's esophagus, and 0.909 for esophageal varices.

CONCLUSION: Esophagoscopy with E.G. Scan™ is a well-tolerated, fast and safe procedure. It has an appropriate diagnostic accuracy for esophageal varices when compared with conventional endoscopy.

Key words: Esophagoscopy; Esophagus; Transnasal; Endoscopy

Core tip: Although esophagogastroduodenoscopy (EGD) is considered the gold standard technique for evaluation of mucosal esophageal diseases, the cost and invasiveness of this diagnostic tool limits its utilization in some patients. Thus, in recent years several endoscopy techniques have been developed as alternatives and less invasive diagnostic tools for evaluating gastroesophageal reflux disease and esophageal varices. Here, in this study we have shown that unsedated esophagoscopy using a novel disposable transnasal esophagoscope (E.G. Scan™) is a safe, well-tolerated, effective and accurate screening tool for esophageal diseases, specifically for esophageal varices.

Aedo MR, Zavala-González MÁ, Meixueiro-Daza A, Remes-Troche JM. Accuracy of transnasal endoscopy with a disposable esophagoscope compared to conventional endoscopy. *World J Gastrointest Endosc* 2014; 6(4): 128-136 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i4/128.htm DOI:

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INTRODUCTION

Esophagogastroduodenoscopy (EGD) is the most effective method to investigate disorders affecting the upper digestive tract. In particular, EGD is the gold standard technique for the evaluation, diagnosis, screening and surveillance of esophageal diseases. Among patients with gastroesophageal reflux disease (GERD) symptoms, up to one-third of patients have endoscopic evidence of erosive esophagitis and up to one-fifth have complicated reflux disease, such as esophageal strictures and Barrett's esophagus (BE)[1,2]. In subjects with portal hypertension, EGD is used for both screening and surveillance purposes because the presence and the size of esophageal varices correlates with severity of liver disease and determines the prognosis[3,4].

Although EGD is widely used and available, the procedure is costly, may be unpleasant, and still has a small but potential risk of complications[5,6]. Frequently, patients are routinely sedated with intravenous diazepam or midazolam, often complemented with a narcotic such as meperidine, fentanyl or propofol[6]. There is a small but definite risk of cardiopulmonary complications, which may be related to a combination of oversedation and pre-existing cardiopulmonary disease[6]. In addition, sedated patients require close monitoring during and after procedures, cannot drive or return to work on the day of the procedure, and may have post-procedure amnesia with poor recall of instructions.

Over the last years, several noninvasive or minimally invasive methods have been proposed as alternatives to conventional EGD for the diagnosis of esophageal diseases, such as esophageal capsule endoscopy (ECE) and ultra-thin small caliber esophagoscopes[7-12]. Several studies have shown that ECE is safe and has an acceptable accuracy for the evaluation of esophageal varices and can be used as an alternative to EGD for the screening of portal hypertension, especially in patients unable or unwilling to undergo EGD[7,9].

Unsedated small-caliber transnasal esophagoscopy offers the possibility of efficient and accurate endoscopic assessment of the esophagus, with less cost and fewer risks compared with sedated upper endoscopy, and can be used as a method to screen for esophageal disease in a primary care population[11-15]. Recently, Chung *et al*[16], in a case series study, reported the use of a novel disposable transnasal esophagoscope, the E.G. Scan™ (IntroMedic Co. Ltd., Seoul, South Korea). This transnasal esophagoscope does not require a large endoscopy system or special equipment for disinfection; it is portable, disposable and well tolerated.

The aim of the study was to assess the feasibility of unsedated routine upper esophagoscopy using the E.G. Scan™ and to compare its optical quality and diagnostic accuracy to that of a standard EGD in the general medical outpatient setting as a screening method for esophageal disease.

MATERIALS AND METHODS

Patients

We performed a prospective study conducted from November 2011 to February 2012 at the Instituto de Investigaciones Medico Biologicas de la Universidad Veracruzana, Veracruz, México. Consecutive patients referred for the evaluation of esophageal diseases were enrolled in the study. Inclusion criteria were: age 20 years or older; reflux symptoms (heartburn, epigastric soreness and/or regurgitation); non-cardiogenic chest pain; and known or suspected esophageal varices. Exclusion criteria included: history or symptoms of severe rhinitis and sinusitis; acute respiratory inflammation at the time of examination; and known abnormal anatomy of the nasal cavity or nasopharynx. All patients provided written informed consent before enrollment and the study received approval from the institution's ethics committee.

Procedures

All conventional EGD and E.G. Scan™ procedures were performed by two experienced endoscopists (J.M.R.T. and A.M.D) after written informed consent was obtained. Randomization was performed by using a computer-generated randomization (www.randomization.com), which allocated patients on a one-to-one basis to the investigator who will perform the EG Scan procedure. Thus if one investigator performed the E.G. Scan™, the other performed the conventional EGD, and investigators were blinded each other. Also, endoscopists were blinded to the indication for endoscopy. The E.G. Scan™ procedure was performed first and 45 min later a conventional sedated endoscopy was performed.

E.G. Scan™: After an overnight fast, patients were referred to the endoscopy unit. For the procedure, patients were seated with their neck at a 30° angle and 2 puffs of a nasal spray containing oxymetazoline hydrochloride, a selective alpha-1 agonist and partial alpha-2 agonist topical nasal decongestant, was sprayed in each nostril (Afrin, Merck Consumer Care, Inc. Mexico). After 5 min, lidocaine hydrochloride 10mg/dose (Xylocaine 10% Pump Spray AstraZeneca, London, United Kingdom) was sprayed into the nasal cavity and oropharynx for topical anesthesia. The endoscope, moistened with Lidocaine HCL jelly 2% (lidocaine hydrochloride 2% 20 mg/mL; Lubricaine, Mexico), was inserted under visual control through the nostril to the pharynx. Upper esophageal sphincter intubation was facilitated by asking the patient to ingest water through a straw with endoscope advancement. No sedatives or antispasmodics were used during the procedure.

The E.G. Scan™ system (first generation) consists of four main subsystems: a probe (containing the camera capsule, bending module and data connector), control-

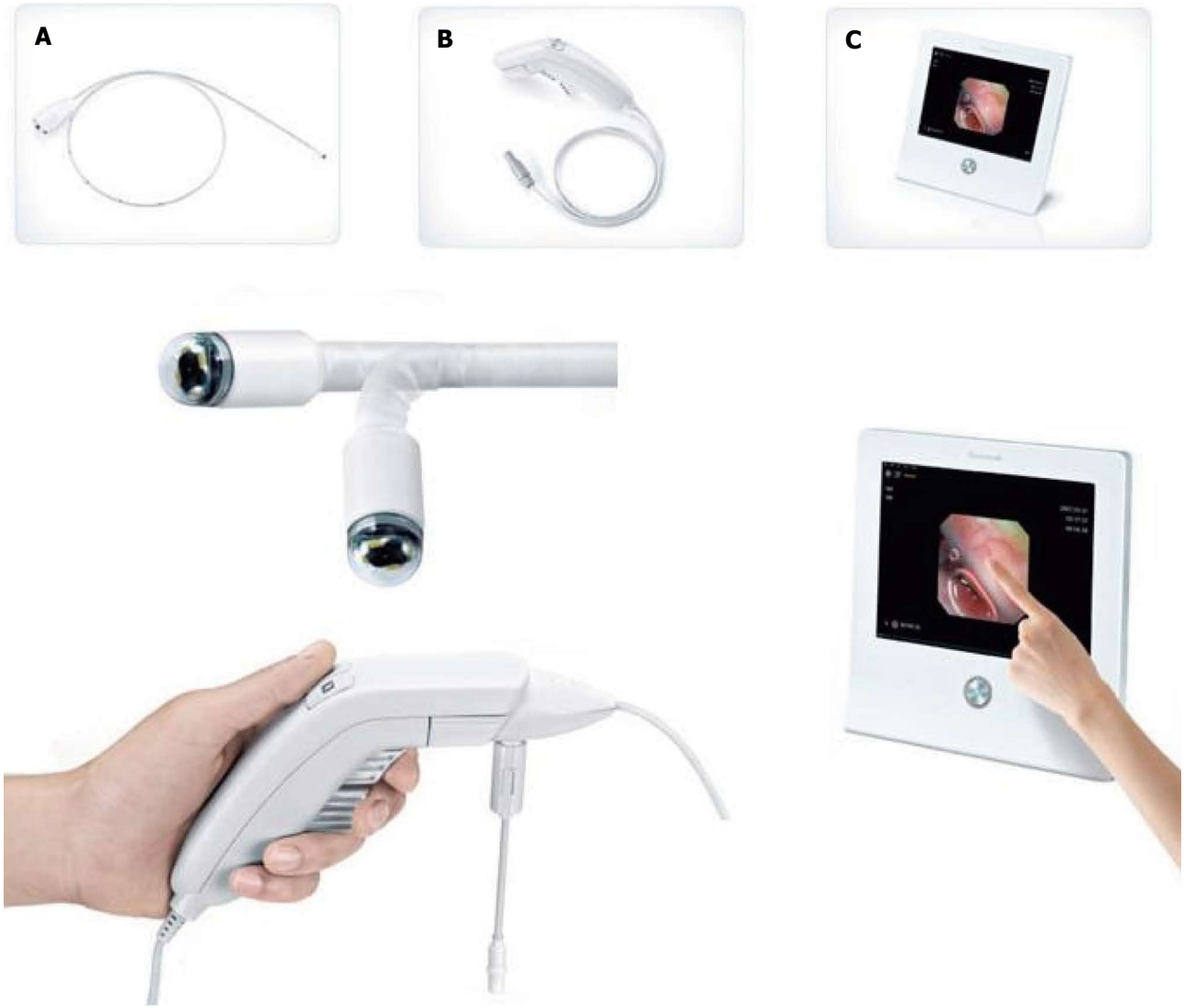

Figure 1 Components of the E.G. Scan™ system (first generation). A: A probe containing the camera capsule, bending module and data connector; B: A controller; C: A display system with computer software to display the images (E. G. View™).

ler, display system and computer software (EG View) to display the images (Figure 1). The connection tube, which does not have suction or an air channel, is 3.6 mm in diameter and the camera capsule at the tip head is 6 mm in diameter. The tip deflection capability is 60° up and 60° down. The camera capsule comprises four white light emitting diodes (LEDs) and a complementary metal-oxide semiconductor (CMOS), with a field of view of 125° and a resolution of 400 × 400 pixels. The probe is disposable. The controller has both freeze-capture buttons and an up-down lever at the handle. The display system consists of a liquid crystal display (LCD) monitor, keyboard and display software (EG View) to allow playback and storage of images taken during the procedure; this system is light enough to carry.

During the procedure, the posterior pharynx, esophagus, esophagogastric junction (EGJ) and proximal stomach were routinely examined. EGJ examination was considered appropriate if at least 75% of the Z-line was visualized[16]. If possible, the mid-stomach, pylorus and duodenum were examined. Any pathological lesions were photographed and recorded on the display system. The investigators documented the duration time of the study, presence or absence of suspected BE, presence or absence of erosive esophagitis, Los Angeles grade of erosive esophagitis (if present), presence or absence of hiatal hernia (documented and measured at the nares in centimeters beginning at the crural pinch distally to the most proximal extent of the gastric folds), esophageal varices were graded according to the size of varices (small or large), the presence or absence of red spots on esophageal varices was also noted, and any other abnormal findings discovered during the study. These findings were recorded on a data sheet. After the procedure, patients completed a written questionnaire to assess their satisfaction with the E.G. Scan™ and level of discomfort for nasal pain and nausea using a 4 point type Likert scale (0 = none, 1 = mild, 2 = moderate and 3 = severe)[17,18].

EGD: Sedated endoscopy was performed with the

Table 1 Baseline characteristics and symptoms *n* (%)

Age (yr, mean, range)	50.12 (18-79)
Gender (male/female)	42/54
Predominant symptoms	
Reflux symptoms	41 (43)
Suspect of esophageal varices	23 (24)
Epigastric pain	14 (15)
Upper GI bleeding	11 (11)
Dysphagia	4 (4)
Weight loss	3 (3)

GI: Gastrointestinal.

Olympus XGIF-160 with patients under local anesthetic with lidocaine spray (Xylocaine; AstraZeneca, United Kingdom) and conscious sedation with midazolam, according to our standard practice. Blood pressure, pulse, cardiac rhythm and oxygen saturation were monitored and recorded every 2 min. In all cases, the endoscope was inserted under visual control through the mouth to the pharynx. The upper esophageal sphincter was crossed under direct vision and the esophagus, stomach and first and second portions of the duodenum were examined as usual. Endoscopic findings were reported using the definitions previously mentioned. Histological confirmation of esophageal biopsies from endoscopically suspected esophageal metaplasia was considered as the "gold standard" for the diagnosis of BE.

Statistical analysis

EGD was considered to be the "gold standard" for the diagnosis of esophageal diseases. According to the Standards for Reporting of Diagnostic Accuracy (STARD) initiative on assessment of diagnostic tests[19], analysis was performed on an intention-to-diagnose (ITD) basis, with all patients enrolled in the trial included in the analysis. The diagnostic performance was expressed in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

At the end of the enrollment period and in a blinded fashion, both endoscopists reviewed the printed images from all E.G. Scan™ studies and interobserver agreement analysis was performed. Concordance among the different E.G. Scan™ observers and between the E.G. Scan™ and EGD final diagnoses was performed using kappa statistics. Our sample size was decided arbitrarily, according to the available material to perform the studies (E.G. Scan™) during the frame time when the study was performed. All other statistics were descriptive and the results are reported in terms of the mean (with 95% confidence interval in brackets) or median and ranges, depending on the distribution of data values. *P* values less than 0.05 were considered statistically significant.

RESULTS

Characteristics of patients at baseline

During the study period, a total of 96 patients (54 women) were included. Mean age was 50.12 years (range 18 to 79). Baseline characteristics and symptoms are described in Table 1. In all cases, we were able to perform esophagoscopy with E.G. Scan™ and the mean duration of the procedure was 5 min (range 3-7.5).

Table 2 E.G. Scan™ and conventional endoscopy esophageal findings

Finding	E.G. Scan™	Conventional EGD
Esophagus		
Esophageal varices (overall)	20	21
Small	5	8
Large	11	13
Erosive GERD	13	29
Grade A-B	10	20
Grade C	2	8
Grade D	1	1
Hiatal hernia	13	33
Barrett's esophagus	8	12
Esophageal carcinoma	2	2
Esophageal angiodysplasia	1	1
Gastric heterotopic mucosa	1	1

EGD: Esophagogastroduodenoscopy; GERD: Gastroesophageal reflux disease.

E.G. Scan™ evaluation

Using the E.G. Scan™ in all cases, the EGJ was evaluated; in 43% the pylorus was visualized and we reach the duodenum in 36% cases. Appropriate evaluation of the EGJ junction was achieved in 95% (n = 91). A total of 58 alterations were detected in the esophagus (Table 2), 49 gastric abnormalities (18 portal hypertension gastritis, 18 mild erythematous gastritis, 10 bile gastropathy, 3 gastric polyps) and 13 duodenal abnormalities (9 duodenitis, findings suggestive of celiac disease in 2, 1 duodenal ulcer and 1 angiodysplasia) (Figures 2-5).

Conventional EGD

Using conventional endoscopy, a total of 99 esophageal diagnoses were made (Table 2). In addition, 71 gastric abnormalities were detected (23 portal hypertension gastritis, 21 erythematous and/or erosive gastritis, 15 bile gastropathy, 8 fundic polyps and 4 fundic varices), and 25 duodenal abnormalities (19 duodenitis, 3 findings suggestive for celiac disease and 3 duodenal ulcers).

Comparison of E.G. Scan™ and EGC

The diagnostic performance of E.G. Scan™ compared to EGD for erosive GERD, Barrett's esophagus, esophageal varices and hiatal hernia is shown in Table 3. Regarding the agreement between E.G. Scan™ and EGD, the kappa values for esophageal diagnoses is shown in Table 4.

E.G. Scan™ interobserver agreement

The mean kappa values for interobserver agreement for each esophageal condition were: for hiatal hernia 0.762 (0.506-1.018); for erosive esophagitis 0.832 (0.606-1.058); for BE 0.554 (0.207-0.901); for esophageal varices 0.903 (0.796-1.011); for large esophageal varices 0.911

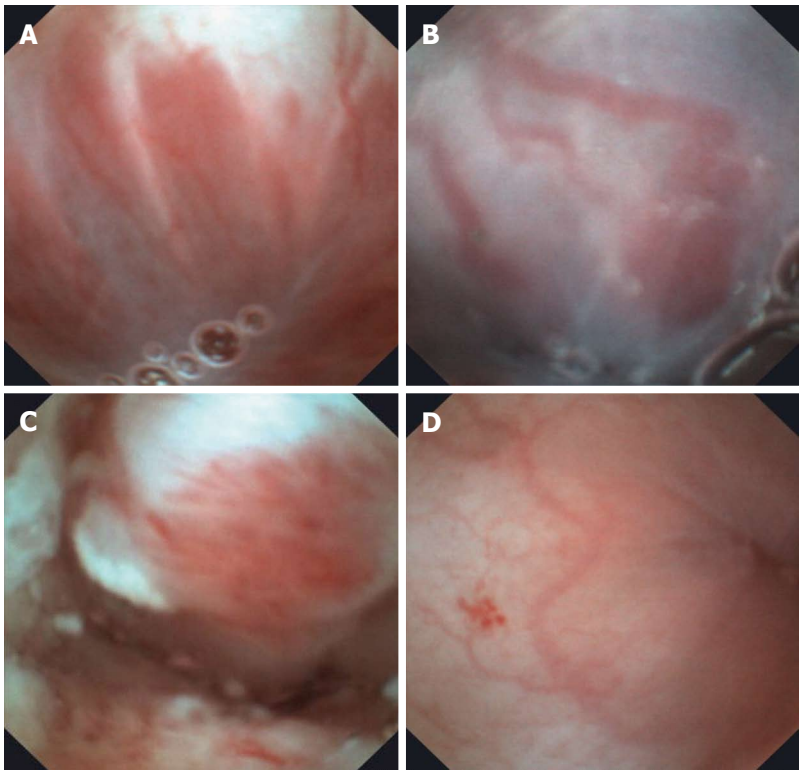

Figure 2 Examples of esophageal diseases detected with the E.G. Scan™. A: Large esophageal varices; B: Medium-small esophageal varices; C: Distal esophageal adenocarcinoma; D: Esophageal angiodysplasia.

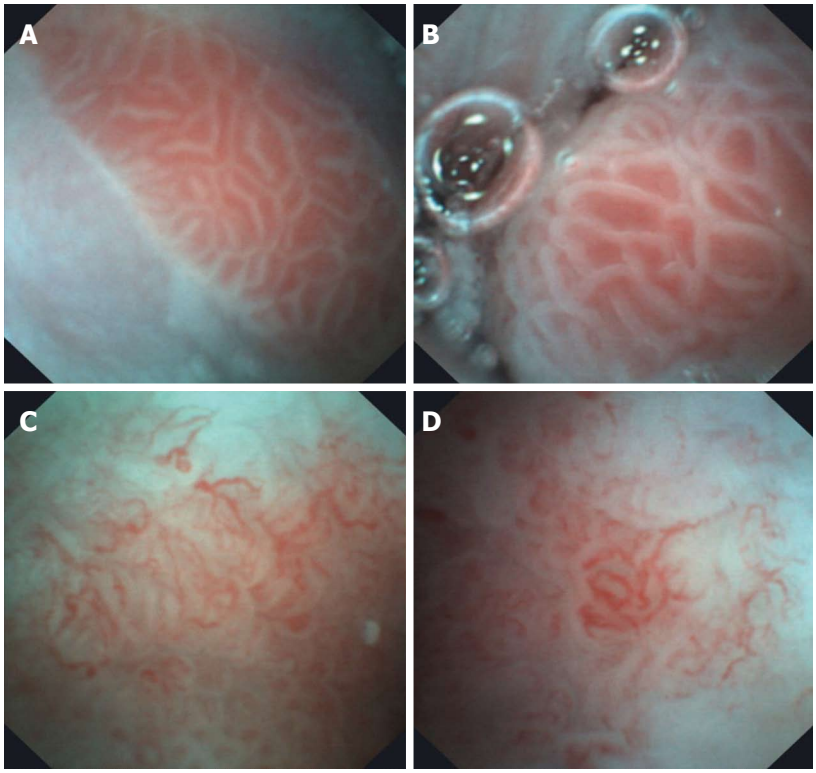

Figure 3 Barrett's esophagus images obtained with E.G. Scan™. A and B: Barrett's without dysplasia; C and D: Barrett's esophagus with low-grade dysplasia.

(0.739-1.083); and for small esophageal varices 0.832 (0.606-1.058).

Patient tolerance

Nasal introduction caused no or only mild pain in 77 of

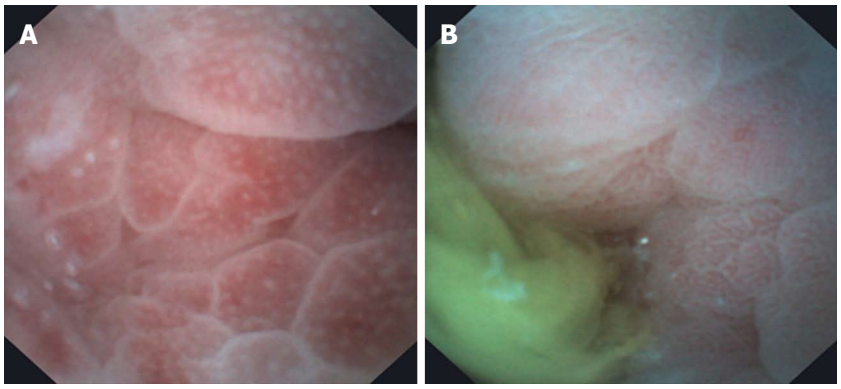

Figure 4 Gastric images obtained with E.G. Scan™. A: Portal hypertension gastropathy; B: Bile reflux gastritis.

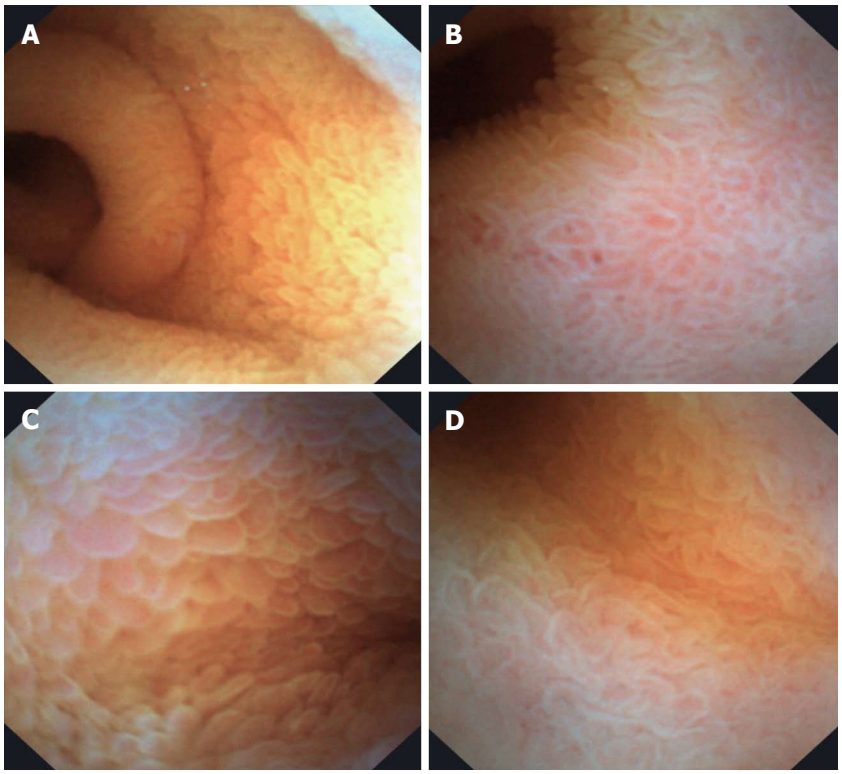

Figure 5 Duodenal images obtained with E.G. Scan™. A: Normal duodenum; B: Mild duodenitis; C and D: Celiac disease.

96 patients (80%) and moderate pain in 19 patients (20%). The majority of patients did not experience nausea (88%).

DISCUSSION

Although EGD is considered the gold standard technique for evaluation of mucosal esophageal diseases, the cost and invasiveness of this diagnostic tool limits its utilization in many patients[6]. Thus, several endoscopy techniques have recently been developed as alternatives and less invasive diagnostic tools for evaluating GERD and esophageal varices[12-16,20].

Here, in this study we have shown that unsedated esophagoscopy using a novel disposable transnasal esophagoscope (E.G. Scan™) is a safe, well-tolerated, effective and accurate screening tool for esophageal diseases, specifically for esophageal varices. In recent years, the use of transnasal endoscopy (TNE) has had a boom and several studies have evaluated the usefulness of this technique. For example, Peery *et al*[20] in one of the largest studies (n = 426) found that TNE is a safe and good method to screen for esophageal disease in a primary care population. In this study, mean examination time with TNE was 3.7 ± 1.8 min and there were no serious adverse events. Our results are similar, but the E.G. Scan ™ has some advantages compared to other transnasal endoscopy systems. Although the tip of the probe is 6 mm in diameter, the connection tube (which does not have suction or an air channel) is 3.6 mm in diameter; thus, the probe is smaller than other TNE (range from 4.1 to 5.9 mm) and could minimize the gag reflex and vomiting. Another advantage is that no disinfection is required be-

Table 3 Diagnostic performance of E.G. Scan™ compared to conventional esophagogastroduodenoscopy

	Prevalence % (95%CI)	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	Accuracy % (95%CI)
Erosive GERD	30.1 (21.5-40.6)	44.8 (27-64)	91 (80.9-96.3)	68.4 (43.5-86.4)	79.2 (68.2-87.3)	77.1 (67.2-84.8)
Barrett's esophagus	12.5 (6.9-21.2)	66.7 (35.4-88.7)	95 (87.6-98.5)	66.7 (35.4-88.7)	95.2 (87.6-98.5)	91.7 (83.8-96.1)
Esophageal varices	21.8 (14.4-31.7)	95.2 (74.1-99.8)	97.3 (89.8-99.5)	90.9 (69.3-98.4)	98.6 (91.7-99.9)	96.8 (90.5-99.1)
Hiatal Hernia	34.4 (25.1-44.8)	39.4 (23.4-57.7)	88.9 (77.8-95)	65 (41-83.7)	73.7 (62.1-82.8)	71.9 (61.6-80.3)

PPV: Positive predictive value; NPV: Negative predictive value; GERD: Gastroesophageal reflux disease.

Table 4 Kappa values for esophageal diagnosis E.G. Scan™ *vs* esophagogastroduodenoscopy

	Kappa value	Standard error of Kappa	95%CI
Esophageal varices	0.910	0.051	0.810-1.010
Large esophageal varices	0.822	0.086	0.653-0.911
Small esophageal varices	0.591	0.151	0.294-0.880
Barrett's esophagus	0.619	0.123	0.378-0.860
Hiatal Hernia	0.398	0.103	0.196-0.600
Erosive esophagitis	0.398	0.100	0.196-0.600

cause the probe is designed for single use and is disposable.

Chung *et al*[16], in the first study published with E.G. Scan™, evaluated 46 patients with suspected or known esophageal disease and found that in almost all cases, the Z line was appropriately evaluated and abnormalities were identified in 27 patients. In this small sample size pilot study, the authors concluded that although E.G. Scan ™ has some technical limitations compared with conventional EGD, its convenience, good tolerance, rapid access, cost-effectiveness and good safety profile indicate that it may be an acceptable alternative to conventional esophagoscopy for surveillance.

Compared to the pilot study by Chung *et al*[16], our study included a larger sample size, we performed the first randomized and blinded evaluation, but most remarkably, we compared the results with the gold standard technique, the EGD. Because conventional endoscopy with sedation may be associated with complications, especially in critically ill patients such as subjects with cirrhosis, the use of an alternative and safe method for evaluating the esophagus, especially in the setting of a screening strategy (*i.e.*, esophageal varices), is needed[5,6]. We found that for esophageal varices (independently of the size), E.G. Scan™ is an excellent option, with sensitivity, specificity and diagnostic accuracy of 95%, 97% and 97%, respectively. These results are similar to that reported by Choe *et al*[21], in a study where 100 cirrhotics were evaluated both by transnasal and standard endoscopy, showing that diagnostic accuracies of transnasal non sedated EGD for detecting esophageal varices, gastric varices and red color signs were 98%, 98% and 96%, respectively. Also, as in the Choe *et al*[21] study, we found that concordance rates on grading esophageal varices were excellent at 95% (κ = 0.91). These results are better than those reported by using endoscopy capsule for detection of esophageal varices[7-9].

With regards to erosive esophagitis diagnosed at upper endoscopy, E.G. Scan™ showed a sensitivity of 45% and specificity of 91%. These results are very similar to those reported by Sharma *et al*[8] in a study comparing ECE versus conventional endoscopy. In a recent study, Shariff *et al*[11] found that using a transnasal endoscope, a correct diagnosis of BE was obtained in 48 of 49 cases compared with the criterion standard, giving sensitivity and specificity of 98% and 100%, respectively. Although in our study the sensitivity was lower (67%), the specificity was 95% for the diagnosis of BE. In another study, Jobe *et al*[12] found that, in a cohort of 274 eligible adults scheduled for endoscopic screening for gastroesophageal reflux symptoms or surveillance of BE in a tertiary care center, the prevalence of BE was 26% using conventional endoscopy and 30% using unsedated small-caliber endoscopy (P = 0.503). In this study, the level of agreement between the two approaches was "moderate" (κ = 0.591). In our study, we found that agreement between E.G. Scan™ and EGD was 0.619. However, E.G. Scan™ misses about half of the cases of erosive esophagitis and one third of patients with Barrett's esophagus. It appears therefore that this version of E.G. Scan™ is not sufficiently sensitive for evaluation of acid reflux evaluation.

It is important to remark that, even although E.G. Scan™ has been developed for esophageal evaluation, in almost 40% of the cases we could reach the pylorus and the duodenum. We could do that because we asked patients to lie down in the left lateral position and then under direct visualization we advanced the probe. As shown in the figures, good quality images from the duodenum of patients with celiac disease and inflammatory duodenitis were obtained.

Regarding tolerability, we found that, as was reported by Chung *et al*[16], most of the patients experienced mild or no symptoms during the procedure and even if they reported mild symptoms, we could perform the evaluation in all cases. An unusual 100% success rate of nasal intubation with this device was found in our study, contrasting with other reports on transnasal endoscopy that present an average of 8% failure rate for nasal intubation due to anatomic nasal limitation or patient intolerance[22,23]. Although the probe shaft is 3 mm, its tip is 6 mm, a little larger than an ultra-slim endoscope, and we believe that the routine use of oxymetazoline hydrochloride, a selective alpha-1 agonist and partial alpha-2 agonist topical, influences such a high success rate for nasal intubation. Previous studies have shown that the use of oxymetazoline for pediatric nasendoscopy is effective,

safe and allows an ease of performance and cooperation of the patients[24]. Although we prepared the patient with an assurance of a successful nasal intubation, we did not use simethicone routinely, a compound that has been used in several studies to improve visibility[25].

Regarding costs, in our country the cost for the E.G. Scan™ device is 8000 USD and each probe costs 140 USD. However, costs can vary among countries and further cost-effectiveness studies are required. Although our study has the strength of a large, blinded evaluation and comparative study with conventional EGD, there are some limitations and technical issues that should be remarked on. The current version of the E.G. Scan™ does not have a channel for air insufflation or water ejection for wash or suction water and bubble air to improve the quality of images. Another major limitation is that it also does not have a biopsy channel to corroborate some conditions, such as BE or malignant lesions. Recently, the manufacturer has provided a new version of the E.G. Scan™ that has an insufflation channel and the bending angle of the tip probe is closed to 180°; thus retroversion at the stomach fundus can now be performed. Nowadays, slim endoscopes have much better quality than in the past with high-resolution images and digital chromoendoscopy and a complete EGD. E.G. Scan™ seems to be an alternative to ultra-slim endoscopes for transnasal examination. In the future, an ideal comparative trial will be performed between E.G. Scan™ and nasogastroscopes.

According to our results, we conclude that E.G. Scan ™ might represent an easy, safe and well tolerated procedure to investigate patients with suspected esophageal varices in the medical outpatient setting.

COMMENTS

Background

Esophagogastroduodenoscopy (EGD) is the most effective method to investigate disorders affecting the upper digestive tract. In particular, EGD is considered as the gold standard technique for the evaluation, diagnosis, screening and surveillance of esophageal diseases. Although EGD is widely used and available, the procedure is costly, may be unpleasant, and still has a small but potential risk of complications.

Research frontiers

Over the last years, a research hotspot has been the development of alternative methods to conventional EGD for the noninvasive or minimally invasive diagnosis of esophageal diseases, such as ultra-thin small caliber esophagoscopes.

Innovations and breakthroughs

Recently, a novel disposable transnasal esophagoscope, the E.G. Scan™ (IntroMedic Co. Ltd., Seoul, South Korea) has been developed. This transnasal esophagoscope does not require either a large endoscopy system or special equipment for disinfection; it is portable, disposable and well tolerated. In our study, we found that that E.G. Scan™ might represent an easy, safe and well tolerated first-line procedure to investigate patients with suspected esophageal varices in the medical outpatient setting.

Applications

Unsedated small-caliber transnasal esophagoscopy offers the possibility of efficient and accurate endoscopic assessment of the esophagus, with less cost and fewer risks compared with sedated upper endoscopy, and can be used as a method to screen for esophageal disease in a primary care population.

Terminology

Esophagogastroduodenoscopy: Esophagogastroduodenoscopy or panendoscopy is a diagnostic endoscopic procedure that visualizes the upper part of the gastrointestinal tract up to the duodenum. It is considered a minimally invasive procedure since it does not require an incision into one of the major body cavities and does not require any significant recovery after the procedure (unless sedation or anesthesia has been used). Esophagoscopy: Esophagoscopy is a procedure in which a flexible endoscope is inserted through the mouth, or more rarely through the nares, and into the esophagus. The endoscope uses a charge-coupled device to display magnified images on a video screen. The procedure allows visualization of the esophageal mucosa from the upper esophageal sphincter all the way to the esophageal gastric junction or esophagogastric junction.

Peer review

This is an interesting and well-designed prospective study that evaluated a new device called E.G Scan™ for endoscopic esophageal examination through the transnasal route compared to conventional EGD, with better results seen with the modified version of the scope. E.G. Scan™ seems to be an alternative to ultra-slim endoscopes for transnasal examination and the ideal comparative trial would have been between E.G. Scan™ and nasogastroscopes. Nowadays slim endoscopes have much better quality than in the past, with high-resolution images and digital chromoendoscopy, and they permit a complete EGD.

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BRIEF ARTICLE

Efficacy of SpyGlass™-directed biopsy compared to brush cytology in obtaining adequate tissue for diagnosis in patients with biliary strictures

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Abstract

AIM: To evaluate the diagnostic yield (inflammatory activity) and efficiency (size of the biopsy specimen) of SpyGlass™-guided biopsy *vs* standard brush cytology in patients with and without primary sclerosing cholangitis (PSC).

METHODS: At the University Medical Center Mainz, Germany, 35 consecutive patients with unclear biliary lesions (16 patients) or long-standing PSC (19 patients) were screened for the study. All patients underwent a physical examination, lab analyses, and abdominal ultrasound. Thirty-one patients with non-PSC strictures or with PSC were scheduled to undergo endoscopic retrograde cholangiography (ERC) and subsequent per-oral cholangioscopy (POC). Standard ERC was initially performed, and any lesions or strictures were localized. POC was performed later during the same session. The Boston Scientific SpyGlass System™ (Natick, MA, United States) was used for choledochoscopy. The biliary tree was visualized, and suspected lesions or strictures were biopsied, followed by brush cytology of the same area. The study endpoints (for both techniques) were the degree of inflammation, tissue specimen size, and the patient populations (PSC *vs* non-PSC). Inflammatory changes were divided into three categories: none, low activity, and high activity. The specimen quantity was rated as low, moderate, or sufficient.

RESULTS: SpyGlass™ imaging and brush cytology with material retrieval were performed in 29 of 31 (93.5%) patients (23 of the 29 patients were male). The median patient age was 45 years (min, 20 years; max, 76 years). Nineteen patients had known PSC, and 10 showed non-PSC strictures. No procedure-related complications were encountered. However, for both methods, tissues could only be retrieved from 29 patients. In cases of inflammation of the biliary tract, the diagnostic yield of the SpyGlass™-directed biopsies was greater than that using brush cytology. More tissue material was obtained for the biopsy method than for the brush cytology method (P = 0.021). The biopsies showed significantly more inflammatory characteristics and greater inflammatory activity compared to the cytological investigation (P = 0.014). The greater quantity of tissue samples proved useful for both PSC and non-PSC patients.

CONCLUSION: SpyGlass™ imaging can be recommended for proper inflammatory diagnosis in PSC patients. However, its value in diagnosing dysplasia was not addressed in this study and requires further investigation.

Key words: Cholangioscopy; Endoscopic retrograde cholangiopancreatography; Primary sclerosing cholangitis; Brush cytology; Biopsy

Core tip: Endoscopic retrograde cholangiography remains the gold standard method for diagnosing biliary tract diseases. However, choledochoscopy with the SpyGlass™ system enables direct visualization of the biliary tract. Furthermore, targeted biopsies can be performed. In our single-center study, the diagnostic yield of SpyGlass™-directed biopsy for inflammatory changes in primary sclerosing cholangitis (PSC) and non-PSC patients was significantly greater than that of brush cytology. The better diagnostic yield strongly correlated with significantly greater amounts of tissue for histological evaluation.

Rey JW, Hansen T, Dümcke S, Tresch A, Kramer K, Galle PR, Goetz M, Schuchmann M, Kiesslich R, Hoffman A. Efficacy of SpyGlass™-directed biopsy compared to brush cytology in obtaining adequate tissue for diagnosis in patients with biliary strictures. *World J Gastrointest Endosc* 2014; 6(4): 137-143 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i4/137.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i4.137

INTRODUCTION

The precise diagnosis of biliary lesions and strictures is of crucial importance in patients with primary sclerosing cholangitis (PSC) or other biliary strictures because malignant tumors of the bile duct frequently have poor prognoses and high recurrence rates. Furthermore, the precise diagnosis of inflammatory activity influences medical and endoscopic treatments and might affect surveillance intervals.

The accurate assessment of bile duct stenosis (malignant *vs* inflammatory *vs* scar) is the ultimate goal of endoscopic retrograde cholangiopancreatography (ERCP) in patients with PSC. However, this differentiation remains challenging because endoscopic retrograde cholangiography (ERC) and other auxiliary fluoroscopy techniques do not permit the reliable diagnostic evaluation of biliary lesions[1,2]. Alternative diagnostic methods, such as endoscopic ultrasonography (EUS) with the use of miniprobes or probe-based endomicroscopy, are still of limited use[3].

Peroral cholangioscopy (POC) provides direct visualization of the biliary tree. This method also permits tissue sampling *via* targeted biopsies. The additional information provided by POC has been reported to change overall patient management and outcomes[4]. Furthermore, POC appears to be useful for clarifying filling defects during ERCP[5]. Recent data suggest that POC provides sufficient resolution and that in combination with biopsy, it can accurately diagnose biliary tract lesions[6]. POC is not a new process, as it has been used since the 1970s[7]. However, when first introduced, the procedure required two investigators, and the fiber-optic image quality was poor[8].

The first single-operator choledochoscopy system was introduced in 2005 by Boston Scientific and is known as the SpyGlass™ direct visualization system. The system enables a single investigator to perform cholangioscopy and targeted biopsies of bile duct abnormalities[9]. After the SpyGlass™ direct visualization system was introduced, its clinical application was reported in several publications. The main aspects addressed in these studies were the accessibility, direct view, and characterization of abnormal biliary lesions[10,11]. A recent study showed that the sensitivity of SpyGlass™ for gross assessment was significantly superior to that of ERC (81% *vs* 53%)[12].

However, ERC remains the gold standard for diagnosing biliary lesions in PSC[13]. Although brush cytology is the preferred investigation method for strictures and PSC-associated lesions, the poor sensitivity has been reported to be a major problem. Cytology achieves fairly good specificity, but its sensitivity is poor (approximately 50%)[14-19]. Cholangioscopy-guided biopsy appears to have the potential to overcome the problems associated with inadequate tissue sampling.

Thus, the aim of the present study was to evaluate the diagnostic yield (inflammatory activity) and efficiency (the biopsy specimen size for histological evaluation) of SpyGlass™-guided biopsy versus standard brush cytology.

MATERIALS AND METHODS

Patient recruitment

From January 2009 to February 2011 at the University Medical Center of Mainz, Germany, 35 consecutive patients with unclear biliary lesions (16 patients) or longstanding PSC (19 patients) were screened for the study. Thirty-one patients were finally included in the study after providing informed consent. All patients underwent a physical examination, lab analyses (Table 1), and abdominal ultrasound prior to ERCP and POC.

Endoscopic system and technique

The Boston Scientific SpyGlass™ and the Boston Scientific SpyScope™ were used for choledoscopy. The choledochoscope was advanced through a standard therapeutic duodenoscope (Pentax ED-3480T, Pentax, Hamburg). The choledochoscope (Boston Scientific™) was passed through the working channel of the "mother" scope (Pentax ED-3480T duodenoscope). All procedures were

Table 1 Patient characteristics

	All patients	PSC	Non-PSC	*P* value
Patients (*n*)	29	19	10	-
Age	(48.9 ± 16.7)	(42.1 ± 13.9)	(61.9 ± 13.9)	0.00172
ALT	(100.2 ± 129.1)	(69.5 ± 41.1)	(155.4 ± 203.9)	0.21921
AST	(74.5 ± 69.0)	(63.7 ± 104.7)	(93.9 ± 107.7)	0.39791
Gamma GT	(411.4 ± 470.7)	(314.7 ± 288.4)	(585.2 ± 674.8)	0.25288
AP	(310.4 ± 212.6)	(285.0 ± 177.3)	(356.0 ± 269.6)	0.46748
Bilirubin	(3.0 ± 4.9)	(2.9 ± 5.0)	(3.3 ± 5.1)	0.83431
CRP	(20.8 ± 32.0)	(15.4 ± 25.9)	(30.3 ± 40.5)	0.31297
Leukocytes	(8.1 ± 3.1)	(8.2 ± 3.3)	(7.7 ± 2.6)	0.66937

PSC: Primary sclerosing cholangitis; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CRP: C-reactive protein.

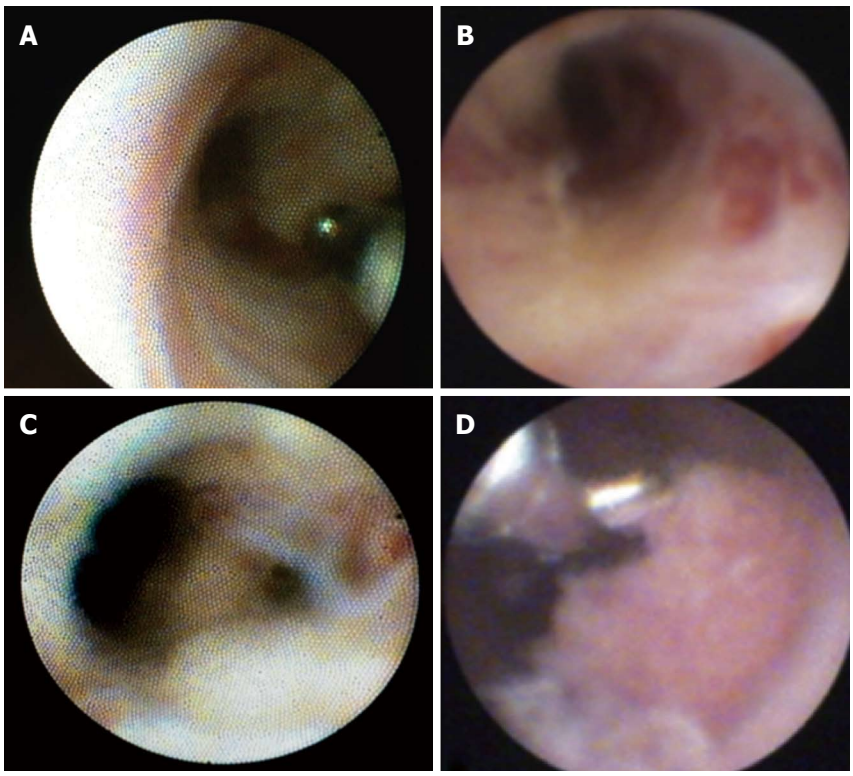

Figure 1 SpyGlass™ visualization of the bile duct. A: A normal bile duct; B: Chronic inflammation, with scars; C: Active inflammation, with mucus fibrin; D: Targeted biopsy of a lesion.

performed using Propofol (1% Disoprivan, AstraZeneca, Switzerland) as sedation.

Before POC, a standard retrograde cholangiogram with biliary sphincterotomy was performed to localize the strictures and to facilitate ductal access and therapy. The choledochoscope was introduced into the bile duct through the guidewire *via* the working channel. For patients in whom the wire could not be advanced beyond a lesion or stenosis, the guidewire was advanced to the stricture under direct visualization of the bile duct whenever possible.

ERCP, POC, and tissue sampling techniques

Standard ERC was initially performed, and any lesions or strictures were localized. Subsequently, POC was performed during the same session. The biliary tree was inspected, and suspicious lesions or strictures were biopsied; at least two or three biopsies per lesion or stricture were taken for histological examination (Figure 1). In addition, brush cytology of the same area was performed with a Cook medical Double Lumen Biliary Brush™ (Cytology). A single pathologist who specialized in biliary pathology graded the biopsy specimens and the brush cytology (T.H.) in a standardized manner. The inflammatory changes were divided into 4 categories (none, low, moderate, high) according to the number of leukocytes. For the biopsies, 5 high-power fields (HPFs, 0.309 mm^2) were observed, and the leukocytes were semiquantitatively analyzed as follows: no activity, < 10 leukocytes/HPF; low activity < 100 leukocytes/HPF; moderate activity > 100 leukocytes/HPF; and high activity > 150 leukocytes/HPF. In the case of the cytological specimens,

Table 2 Quantity of material

		Brush			Total
		Small	Moderate	Sufficient	
Biopsy	Small	3	4	0	7
	Moderate	6	4	2	12
	Sufficient	9	1	0	10
Total		18	9	2	29

Quantity of material by method. Bowker's test for symmetry of contingency tables yielded a *P*-value of 0.021.

Table 3 Inflammatory activity

		Brush				Total
		None	Low	Moderate	High	
Biopsy	None	0	1	0	0	1
	Low	0	11	0	0	11
	Moderate	0	8	0	0	8
	High	1	6	0	2	9
Total		1	26	0	2	29

Signs of inflammation by method. Bowker's test for symmetry of contingency tables yielded a *P*-value of 0.014.

semiquantitative evaluation revealed the following activity levels: none, < 5 leukocytes/HPF; low, < 50 leukocytes/HPF; and high, > 50 leukocytes/HPF. The quantity of specimens was rated as low, moderate, or sufficient, according to the cell number in an HPF (0.306 mm^2); in the case of cytology, the quantities were as follows: low, < 10 cells/HPF; moderate, < 20 cells/HPF; and sufficient, > 50 cells/HPF). In biopsy specimens, either the number of specimens (low, one tissue fragment; moderate, at least two tissue fragments; sufficient, at least three tissue fragments) or the number of mucosal folds/villi was encountered (low, one villus; moderate, at least two villi; sufficient, at least three villi).

Ethical considerations

The ethics committee of Rheinland-Pfalz, Germany, approved this study (No. 837.432.07 (5967)).

Statistical analysis

Practical limitations allowed us to collect material from 31 patients; 2 samples did not meet our quality criteria. The material collection proved to be sufficient to detect the differences between the two groups. Statistical analysis was performed using the R statistical language. Bowker's test was used to reject the null hypothesis of symmetry in contingency tables (Tables 2 and 3):

$$\sum_{i<j} \frac{(n_{ij} - n_{ji})^2}{n_{ij} + n_{ji}}$$

, where B is χ^2 distributed with $[n(n-1)]/2$ degrees of freedom.

All reported *P* values are the result of a data exploration process.

RESULTS

All 31 patients underwent brush cytology and biopsy. No procedure-related complications were encountered. However, for both methods, tissues could be retrieved from only 29 patients. In one patient, SpyGlass™ failed to obtain any tissue material; in another patient, no cytological specimens could be obtained using brush cytology.

The patient and laboratory characteristics are summarized in Table 1. Twenty-three of the 29 patients were male, and the median patient age was 45 years (range, 20-76 years). Nineteen patients had known PSC, and 10 showed non-PSC strictures. The patient characteristics did not significantly differ between the two groups. Four patients had a suspicion of malignant strictures during endoscopy that was not confirmed by histologic results.

The biopsy method revealed significantly more tissue material ($P = 0.021$) than the brush method (Table 2, Figure 2). In 10 patients, the number of biopsy specimens was sufficient; by contrast, only 2 patients demonstrated sufficient numbers of specimens by brush cytology. In 27 patients, no or little inflammatory activity was detected using the brush method, compared to 12 patients using the biopsy method. Using SpyGlass™-directed biopsy, a greater degree of inflammatory activity (classified as moderate or high) was observed in 17 of 29 (58.62%) patients ($P = 0.014$) (Table 3). Brush cytology failed to reveal any significant signs of inflammation because of the paucity of material. A common characteristic of the two techniques was that a greater quantity of test material predicted stronger signs of inflammation. The subgroup analysis between the PSC and non-PSC patients did not reveal any significant differences in the assessment of inflammatory activity with regard to the biopsy or brush method, respectively (Tables 4, 5). Neither brush cytology nor biopsy detected any malignant strictures or dysplasia in the patients.

The brush method demonstrated a positive correlation between the amount of test material and the characteristics of inflammation. This method typically produced little study material and revealed only a few features of inflammation. SpyGlass™-directed biopsy showed moderate or high levels of inflammation in 17 of 29 cases.

A significantly greater quantity of material was obtained with the biopsy-directed procedure. Brush cytology showed adequate signs of inflammation in two cases (Table 2). We observed no differences in the outcomes of the patients with or without PSC. Furthermore, no significant difference was noted in the patients with elevated laboratory parameters of inflammation with regard to the histopathological signs of inflammation.

DISCUSSION

SpyGlass™ is a single-operator system that allows direct visualization of the biliary and pancreatic tracts[9,20]. SpyGlass™ provides significantly greater sensitivity to clarify biliary strictures compared to ERCP[12,21,22]. The largest study in the literature (comprising nearly 300 patients)

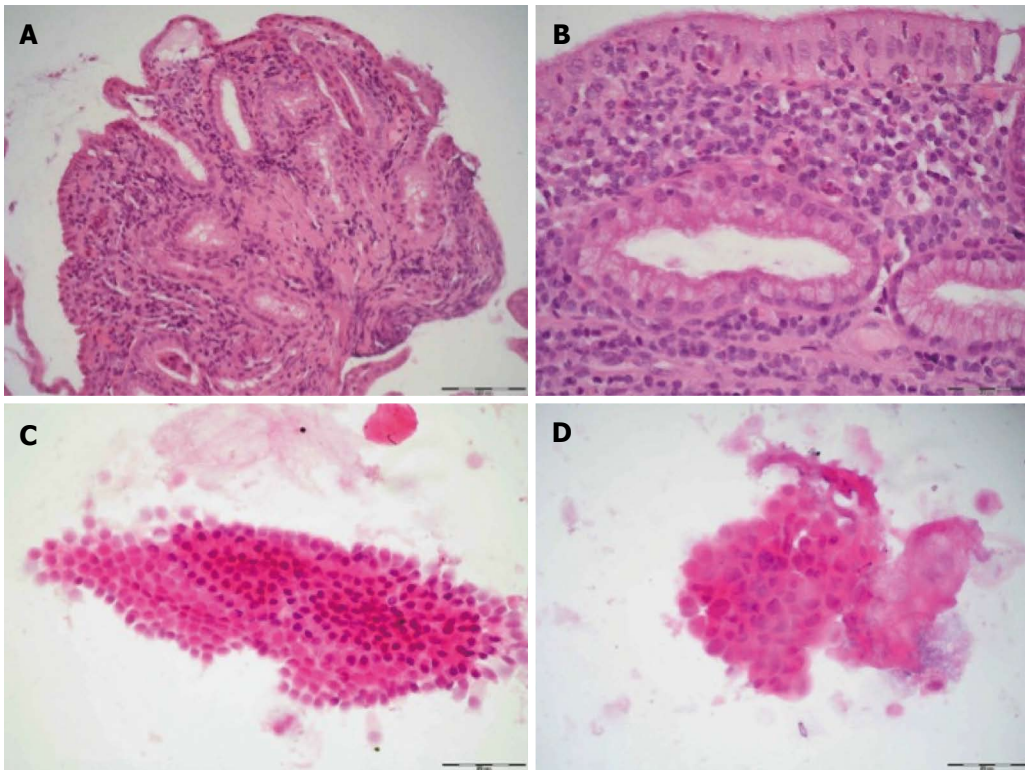

Figure 2 Comparison of biopsy and brush cytology. Histological examination of the biopsy (A, B) shows parts of the bile duct wall with regularly shaped epithelium (original magnification, × 100 A, × 400 B). A detailed view in B confirms marked inflammation with numerous lymphocytes and neutrophilic granulocytes infiltrating the bile duct mucosa. Cytological analysis of the same patient was in the upper figures (original magnification C, D), demonstrating regular epithelial cells and few leukocytes.

showed that SpyGlass™ could visualize 96% of all strictures and that 88% of the identified strictures or lesions could be successful biopsied[23]. Other studies reported a higher diagnostic value of SpyGlass™-guided biopsy compared to brush cytology[24-26]. However, to date, the diagnostic yield for PSC has not been clarified. Thus, we investigated the diagnostic value of SpyGlass™-directed biopsy versus brush cytology in patients with or without PSC. Furthermore, we evaluated whether the biopsy or brush cytology characteristics differed between PSC and non-PSC patients. We clearly demonstrated that SpyGlass™-guided biopsy obtained greater quantities of tissue specimens and provided a more accurate diagnosis of inflammatory changes. This result is important because the degree of inflammation might alter the medical treatment or refine the surveillance of PSC patients.

Our study focused on the amount of tissue obtained and the presence of inflammatory changes. Although malignant changes were suspected in four of our patients during endoscopy, the specimens could not confirm dysplasia or carcinoma. However, malignancies have been identified using SpyGlass™, with a reported accuracy of 77% in patients with suspected cholangiocarcinoma[4,25-28]. Our study could not clarify whether SpyGlass™ is beneficial in identifying PSC-associated dysplasia.

In our study, biopsy specimens were obtained using SpyGlass™ in 28 of 29 cases (96.5%). This percentage is greater than that previously reported[11], which might be because we performed at least 2-3 passes of the biopsy forceps (Spybite™) at the area of interest.

Brush cytology often failed to reveal signs of inflammation because of the paucity of material. The most important result of our study was that tissue acquired by directed biopsy was associated with greater signs of inflammation that allowed a more precise diagnosis because SpyGlass™-directed biopsy acquired a greater amount of sample, at quantities adequate for analysis. Pathological examination improved the diagnosis of inflammation by the amount of specimens. This result occurred significantly more often in the biopsied specimens. These data are relevant with regard to patients with unknown biliary strictures and concur with another study in which the initial working diagnosis was modified after a SpyGlass™ investigation in 68.9% of patients with biliary strictures[29]. Specific risk populations (*e.g.*, patients with PSC or prolonged chronic inflammation of the bile duct) are subject to an increased risk of cancer[30,31]. As POC provides direct information about the bile duct, it may serve as an important and informative extension of ERC[22].

Note that there were no complications related to the SpyGlass™ examination. In addition to the expected result of improved detection of inflammation in SpyGlass™-directed biopsy, we also demonstrated that the method was easy and safe, as previously reported[32].

The present study had some limitations. First, we had to perform brush cytology after biopsy, and the influence of the quantity of the brush cytology specimens remains unknown. Second, this study was performed at a single

Table 4 Inflammatory activity in primary sclerosing cholangitis patients

		Brush				Total
		None	Low	Moderate	High	
Biopsy	None	0	0	0	0	0
	Low	0	6	0	0	6
	Moderate	0	4	0	0	4
	High	1	6	0	2	9
Total		1	16	0	2	19

Signs of inflammation (by method) for the patients diagnosed with PSC. Bowker's test for symmetry of contingency tables yielded a *P*-value of 0.088.

Table 5 Inflammatory activity in non-primary sclerosing cholangitis patients

		Brush				Total
		None	Low	Moderate	High	
Biopsy	None	0	1	0	0	1
	Low	0	5	0	0	5
	Moderate	0	4	0	0	4
	High	0	0	0	0	0
Total		0	10	0	0	10

Signs of inflammation (by method) for the patients who were not diagnosed with PSC. Bowker's test for symmetry of contingency tables yielded a *P*-value of 0.544.

center with a limited number of patients. Third, a single pathologist performed all the histopathological examinations.

In conclusion, the diagnostic yield of SpyGlass™-directed biopsy for inflammatory changes in PSC and non-PSC patients was significantly greater than that of brush cytology. The better diagnostic yield strongly correlated with the greater amount of tissue specimens obtained from the SpyGlass™-directed biopsy. A total of 2-3 biopsies must be obtained from suspicious areas in the biliary tract. Further studies are needed to fully clarify the benefit of the better inflammatory diagnosis in PSC and to investigate the potential of SpyGlass™ in diagnosing PSC-associated dysplasia.

COMMENTS

Background

Patients with primary sclerosing cholangitis (PSC) suffer from chronic and relapsing inflammation of the biliary tract. Endoscopic retrograde cholangiopancreatography is recommended procedure to stage the disease and to clarify inflammatory strictures. Spyglass™ as a single operator cholangioscopy system provides direct visualization of the biliary tract with the possibility of direct biopsies.

Research frontiers

Cholangioscopy is basically not a new process. It has been introduced since the 1970´s as a so-called mother-baby endoscopy technique, in which a thin choledochoscope (baby-scope) was pushed through the instrumentation channel of the duodenoscope (mother-scope) during the endoscopic retrograde cholangiography (ERC). The procedure required two investigators and the quality of the fiber-optic images was poor. The first single-operator choledochoscopy system was introduced in 2005 by Boston Scientific, and is known as the SpyGlass™ direct visualization system.

Innovations and breakthroughs

Precise diagnosis of biliary lesions and strictures is still difficult but of crucial importance for the patients. However, neither ERC nor other auxiliary fluoroscopy-techniques permit reliable diagnostic evaluation of biliary lesions. The gold standard for the diagnosis of biliary lesions, especially in PSC, is still ERC. A recent study showed that the sensitivity of SpyGlass™ for gross assessment was significantly superior to that of ERC (81% *vs* 53%) and biliary strictures could be significant better characterized. Furthermore the SpyGlass™ system allows optical guided biopsy sampling with definite histologic diagnosis and high accuracy.

Applications

This study indicates that the diagnostic yield of SpyGlass™-directed biopsies for inflammatory changes in PSC and non-PSC patients is significantly higher than that of brush cytology. The better diagnostic yield is strongly correlated with the larger amount of tissue specimens, which can be obtained with SpyGlass™ directed biopsies.

Terminology

The SpyGlass System was developed to overcome the limitations of the so called traditional cholangioscopy. Integrated irrigation channels and a 1.2 mm diameter therapeutic channel make for the first time optical guided biopsies and therapeutic stone management possible. Thus, this system enables for a single investigator during ongoing ERC to perform targeted biopsy of bile duct lesions and to perform laser therapy of complicated bile duct stones.

Peer review

This study is well conducted even if only a few patients were included. In this study the advantages of direct cholangioscopy with the possibility of using a single operator cholangioscopy and with the possibility of direct biopsies are well described. The results showing significant advantages of biopsy versus brush cytology in grading inflammation and non-inflammatory changes in the bile duct.

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CASE REPORT

Rare presentation of primary (AL) amyloidosis as gastrointestinal hemorrhage without systemic involvement

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Abstract

We are reporting a rare case of a patient with primary (AL) amyloidosis presenting with an acute non-variceal upper gastrointestinal hemorrhage in the absence of other systemic involvement. The case report involves a 58-year-old woman with significant cardiac history and hereditary blood disorder who came in complaining of abdominal pain and coffee-ground emesis for two days. Computed tomography (CT) scan of the abdomen and pelvis with contrast revealed segmental wall thickening of the proximal jejunum with hyperdense, heterogenous luminal content. Similar findings were evident in the left lower small bowel region, suspicious for small bowel hematoma and the possibility of intraluminal clots. Esophagogastroduodenoscopy performed post resuscitation showed punctate, erythematous lesions throughout the stomach as well as regions of small bowel mucosa that appeared scalloped, ulcerated, and hemorrhaged on contact. Despite initial treatment for immunostain-positive focal cytomegalovirus gastritis, follow-up esophagogastroduodenoscopy after two months continued to demonstrate friable and irregular duodenal mucosa hinting at a different underlying etiology. Pathology reports from analyses of biopsy samples highlighted infiltration and expansion of the lamina propria and submucosa. Subsequent staining with congo red/crystal violet and appropriate subtyping established the diagnosis of AL (kappa)-type amyloidosis. The significance of this case lies in the fact that our patient did not have the typically seen diagnostic systemic involvements-namely of heart and kidneys-usually seen in primary (AL) amyloidosis patients. It was the persistent endoscopic findings and biopsy results which gave clues to the physicians regarding the possibility of an abnormal protein-deposition entity.

Key words: Primary amyloidosis; AL amyloidosis; Gastrointestinal hemorrhage; Endoscopic finding; Endoscopic biopsy; Upper gastrointestinal bleeding; Amyloid deposition; Gastric/intestinal mucosa; Mucosal inflammation

Core tip: This case report of a 58-year-old African-American woman with coffee-ground emesis highlights a rare instance where AL (kappa)-type amyloidosis presents as gastrointestinal hemorrhage in the absence of clinical disease elsewhere in the body. Esophagogastroduodenoscopy initially revealed punctate, erythematous lesions throughout the stomach as well as regions of small bowel mucosa that appeared scalloped, ulcerated, and hemorrhaged on contact. Patient was treated for cytomegalovirus gastritis based on biopsy results. However, repeat enteroscopy continued to demonstrate friable and irregular duodenal mucosa with pathology highlighting infiltration and expansion of the lamina propria and submucosa. Appropriate staining and sub-

typing established AL (kappa)-type amyloidosis.

Ali MF, Patel A, Muller S, Friedel D. Rare presentation of primary (AL) amyloidosis as gastrointestinal hemorrhage without systemic involvement. *World J Gastrointest Endosc* 2014; 6(4): 144-147 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i4/144.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i4.144

INTRODUCTION

Primary (AL) amyloidosis is an infrequent disorder and the exact incidence is unknown. In the United States, there is roughly 6 to 10 cases per million person-years[1]. The median age at diagnosis is 64 years. There is a male predominance with men accounting for 65% to 70% of patients[2].

Amyloidosis involves the extracellular deposition of protein fibrils. Primary (AL) amyloidosis, as diagnosed in our patient, is associated with monoclonal light chains in serum and or urine. The kidneys and heart are the most commonly involved organs. However, the nervous system, lungs, liver, soft tissue and the gastrointestinal (GI) tract can be involved as well[3].

The occurrence of clinically evident gastrointestinal involvement depends on the type of amyloidosis. While as many as 60% of patients with reactive amyloidosis display gastrointestinal disease, it appears far less common in AL amyloidosis.

CASE REPORT

A 58-year-old African-American woman with history of sickle cell disease, atrial fibrillation, Wolff-Parkinson-White syndrome and AICD presented with epigastric pain, coffee-ground emesis for 2 d. Patient denied nausea, early satiety, constipation, or dysphasia. She was found to have a hemoglobin level of 4.5 g/dL and was positively orthostatic, consequently requiring fresh frozen plasma (FFP) and multiple units of packed red blood cells (RBCs). The patient was started on continuous IV proton pump inhibitor (PPI) and admitted to ICU for close monitoring.

Computed tomography (CT) abdomen/pelvis with contrast showed segmental wall thickening of the proximal jejunum with hyperdense, heterogenous luminal content. Similar findings were evident in the left lower small bowel region, raising suspicion for small bowel hematoma with the possibility of intraluminal clots. Esophagogastroduodenoscopy post-resuscitation revealed punctate, erythematous lesions throughout the stomach (including the cardia) as well as regions of small bowel mucosa that appeared scalloped, ulcerated, and hemorrhaged on contact. Biopsies suggested marked acute duodenitis with blood, fibrin, and acute inflammatory exudates, indicative of the bleeding site (Figure 1B). Immunostains of these

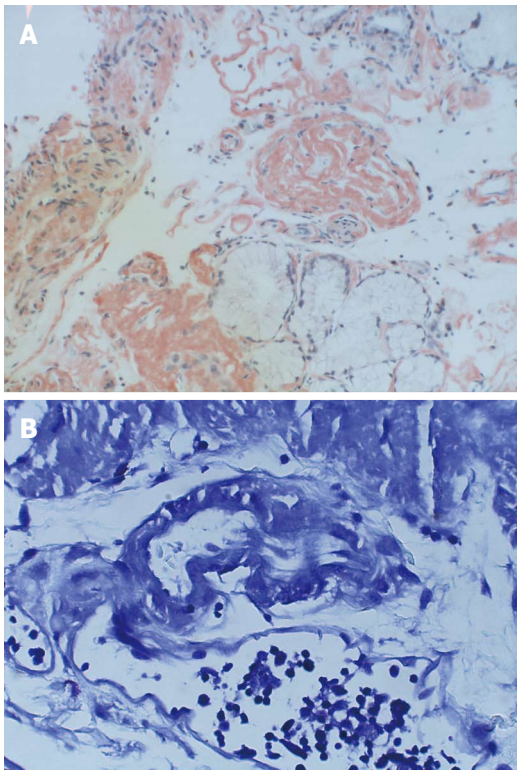

Figure 1 Small bowel biopsies with multiple immunostains confirming amyloid deposition. A: Duodenal Biopsy; Congo Red (× 20); Infiltration and expansion of the lamina propria and submucosa by amyloid deposition staining positive for Congo-Red; B: Small Bowel Biopsy; Crystal Violet (× 40); Marked acute duodenitis with blood, fibrin, and acute inflammatory exudates, suggestive of bleeding site. Crystal Violet stain positive for amyloid.

samples indicating focally active gastritis were positive for cytomegalovirus (CMV). Treatment with Valganciclovir (900 mg every 12 h) for 21 d was initiated.

A repeat enteroscopy 2 mo later to assess for healing, continued to demonstrate friable and irregular duodenal mucosa (Figure 2). There was oozing from areas of scope contact and biopsy sites. Argon plasma coagulation was used to achieve hemostasis. Pathology underlined infiltration and expansion of the lamina propria and submucosa (Figure 1A) in addition to eosinophilic deposition around blood vessels (Figure 3). Immunostain was negative for CMV. Congo Red/Crystal Violet staining however, was positive, and appropriate subtyping subsequently established AL (kappa)-type amyloidosis.

DISCUSSION

The clinical diagnosis of gastrointestinal amyloidosis can be challenging in patients in whom the presence of this disease entity has not yet been established. Rarely does AL-amyloid present in the gastrointestinal tract as acute GI hemorrhage without other systemic symptoms[4]. Cardiac involvement, seen in 90% of the cases, is marked by congestive heart failure (CHF) and arrhythmias due to restrictive cardiomyopathy[5]. Diastolic dysfunction contributing to heart failure is apparent on echocardiography. Our patient had normal left ventricular systolic function

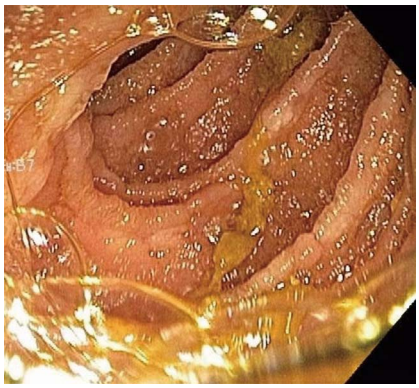

Figure 2 Second segment of the duodenum demonstrating notched mucosal appearance.

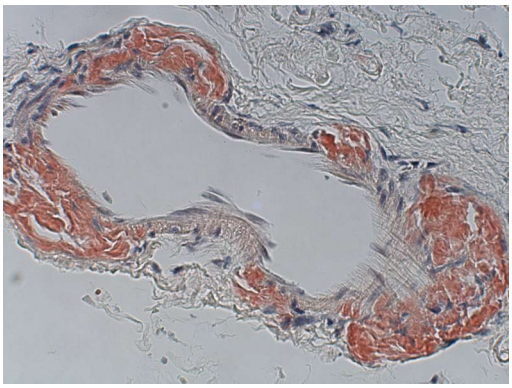

Figure 3 Colon Biopsy; Congo Red (× 40). Fragments of colonic mucosa and separate fragments of submucosa with eosinophilic material deposited around blood vessels, consistent with amyloid deposition. Congo Red stain positive.

and although she had abnormal left ventricular diastolic function, her E/A ratio was 1.3. The E/A ratio is usually greater than 2.0 in the restrictive cardiomyopathy associated with amyloidosis[6]. Additionally, the patient did not display any clinical signs of heart failure (*e.g.*, lower extremity swelling of jugular venous distention). Renal insufficiency and/or nephrotic syndrome was also lacking in our patient.

Gastrointestinal manifestations appear to be less common in AL amyloidosis, with biopsy diagnosed disease and clinically apparent disease occurring in only 8% and 1% respectively of 769 patients in a retrospective review[7]. Despite the infrequency of gastrointestinal manifestations, the small intestine is the site of greatest deposition when there is involvement. Duodenal amyloidosis results in scalloped edges, duodenitis, ulcers, masses, hypotonia, and dilatation[8-10]. Endoscopic findings commonly include a fine granular appearance, polyps, erosions, ulcerations, and mucosal friability[11]. Clinical signs and symptoms may include hemorrhage, obstruction, and infarction amongst others.

Bleeding occurs as a presenting symptom in 25%-45% of patients with amyloidosis and may be caused by ischemia or infarction, by ulceration or an infiltrated lesion, or from generalized oozing without a particular source[12]. Endoscopy shows diffuse involvement, such as esophagitis and gastritis, more often than discrete lesions, as observed in our patient.

COMMENTS

Case characteristics

A 58-year-old African-American woman with history of sickle cell disease, atrial fibrillation, Wolff-Parkinson-White syndrome and AICD presented with epigastric pain, coffee-ground emesis for 2 d.

Clinical diagnosis

Tenderness to palpation in the epigastric region on abdominal exam.

Differential diagnosis

Multiple myeloma, chronic lymphocytic leukemia, Amyloidosis, Gastritis.

Laboratory diagnosis

Hemoglobin 4.5 g/dL; Hematocrit 13.4%; INR 2.15.

Imaging diagnosis

CT scan of the abdomen and pelvis showed marked segmental wall thickening of the proximal jejunum and parts of the small bowel, with hyperdense, heterogenous walls/luminal content.

Pathological diagnosis

Small bowel biopsy (duodenum) showed infiltration and expansion of the lamina propria and submucosa by Congo-red and crystal violet-positive amyloid.

Treatment

Symptom control, *e.g.*, blood transfusion/fluid resuscitation, monitoring vitals.

Related reports

AL-amyloid rarely presents in the gastrointestinal tract as acute GI hemorrhage without other systemic symptoms.

Term explanation

The E/A ratio is a marker of the function of the left ventricle of the heart and is calculated on echocardiography with abnormalities indicative of diastolic dysfunction.

Experiences and lessons

This case report highlights the importance of endoscopic findings and biopsy revelations in making a diagnosis of amyloidosis in patients without other systemic manifestations.

Peer review

The paper is well written and reports an interesting case.

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FIELD OF VISION

Telementoring in education of laparoscopic surgeons: An emerging technology

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Abstract

Laparoscopy, minimally invasive and minimal access surgery with more surgeons performing these advanced procedures. We highlight in the review several key emerging technologies such as the telementoring and virtual reality simulators, that provide a solid ground for delivering surgical education to rural area and allow young surgeons a safety net and confidence while operating on a newly learned technique.

Key words: Telemedicine; Telementoring; Videoconference; Surgical education; Minimal invasive surgery

Core tip: Telemedicine is becoming used more and more in today's surgical practice. We highlight a new low cost telementoring prototype we developed that allows the delivery of better surgical education and delivering specialized expertise to rural areas. Telemedicine is a global term for a computer technology that allows medical information exchange from one location to another *via* telecommunication. Telemedicine helps in eliminating the distance barriers and provides medical expertise to rural communities.

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COMMENTARY ON HOT TOPICS

Telemedicine is a global term for a computer technology that allows medical information exchange from one location to another *via* telecommunication. Telemedicine helps in eliminating the distance barriers and provides medical expertise to rural communities. There are several definitions of telemedicine, but a commonly used definition was proposed by The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES): "The practice of medicine and/or teaching of the medical art, without direct physical physician-patient or physician-student interaction, *via* an interactive audio-video communication system employing tele-electronic devices"[1].

Populations around the world are expanding; with the population of the United States of America expected to increase 50% by 2050, yet between 1980 and 2005 there was no increase in medical school enrollments. The funding of all postgraduate positions including

general surgery has not changed significantly in the past 20 years[2]. Unless the rate at which general surgeons are trained increases, the number of general surgeons per population will continue to decline[3]. In 2003, Etzioni *et al*[4] found that as a result of an expanding/aging population, there would be a 31% increase in surgical work between 2001 and 2020. More recently, Williams *et al*[5] estimated that in 2030 there would be a 9% shortage in the general surgical workforce, with greater shortages in other surgical specialties. Due to the future shortage of surgeons, novel ways of surgical education should be explored. Surgical telementoring may be a solution to enhance and improve surgical education.

Surgical technique and technology has rapidly advanced, especially in the areas of laparoscopy. These advanced procedures of minimally invasive and minimal access surgeries are being performed by a greater number of surgeons. Learning to perform a new laparoscopic surgical technique can be extremely challenging, as it relies on the local mentor's knowledge, skill level, and ability to communicate instructions to guide surgical students in their initial experience[6]. Sixty years ago, Gershon-Cohen began to send X-rays using facsimiles over a distance of 28 miles by using simple telephone service to transmit the images[7]. In 1962, DeBakey pioneered the field of telemedicine with the first video conferencing (VC) demonstration of open-heart surgery (Houston, Texas, United States) transmitted overseas *via* satellite, allowing real time viewing of an aortic valve replacement by medical staff in Geneva (Switzerland)[8]. Advances in both communication and computing technologies have allowed the development of a low cost and reliable solution for conveying telemedicine over great distances[2,9,10].

RESEARCH

This paper is a semi systematic review. It is based on a PubMed search as well as the experience from the co-authors who are core researchers at the Norwegian National Centre of Telemedicine in the use of videoconferencing (KAM, HRHP, ROL). The search terms were: Telementoring, tele-mentoring, videoconferencing, video-conferencing. These terms were then combined with the search terms such as laparoscopic surgery and surgical education. Selected key articles and studies were chosen to emphasize the role of videoconferencing and telementoring in surgical education.

The objective of this paper is to explore the use of telementoring in surgical education.

VIDEO CONFERENCING

VC has been in use in medical and surgical fields for many years. In recent years the technology has improved and become more accessible. Today almost every personal computer is able to perform basic videoconferencing at a low cost with relatively high quality.

Needed video conferencing equipment

The International Telecommunication Union (ITU) has defined several technical standards for videoconferencing equipment. ITU defined a standard to establish if the equipment can communicate properly and handle the data load sufficiently. Clear regulations for sound, video, parallel video streams, and data encryption as well patient security, confidentiality, and privacy were set under those standards[11].

Five methods for data transmission during videoconferencing are available today (Table 1): satellite communication, Internet Protocol (IP)-based communication, Integrated Services Digital Network (ISDN), third-generation (3G) and forth-generation (4G/LTE) Mobile phones.

VC in surgical education and postoperative follow-up

VC has been in use among different specialties for many years. Common use of VC is in post-operative treatment and follow-up due to the relatively low costs, advancements in technology and the development of network infrastructures. Reported results of telementoring which is described as a natural fit in surgery[12], are improved surgical practice, education, treatment and postoperative care[13].

Remote presents and telementoring: The RP-7 (RP-7; Intouch Health, Santa Barbara, California) is an example of a high-end robotic remote presence system that can be controlled by a portable personal computer linked *via* Internet connection. Its dimensions are 165 cm in height and 63 cm × 76 cm at its base, comparable in size to that of an average human. The head of the robot is equipped with two advanced digital cameras, audio microphone and sophisticated engineering allows a real-time, two-way audio-video link. In addition the robot is highly maneuverable and allow a wide range of motions, *e.g.*, panning and tilting[10].

Sereno *et al*[14] Described a successful experiment using the previous version of the remote presence robot the RP-6 (predecessor to the RP-7). They have used two type of mentoring methods (1) the standard assistance called "active onsite mentoring" where the expert surgeon provides assistance with verbal instructions and practical support by manipulating or changing the position of instruments and camera when necessary (Figure 1); and (2) "Passive onsite mentoring" where the expert limited his or her support to verbal assistance without using hands to correct the positioning of instruments or camera (a method that is more similar to the one provided by the robot). They concluded that even though "human" mentoring is considered superior over remote "robotic" mentoring, the difference between the two groups was not as large as they had expected. Although it is clear that a remote presence robot may not replace the local mentors, they have been shown that it is a valuable tool in telementoring minimally invasive procedures[14].

Table 1 Technical solutions for data transmission during video-communication[8]

Type of technology used for VC communication	Bandwidth	Pros	Cons	Suitable for	Price
Satellite	⩾ 128 kb/s	Portable Worldwide use (*i.e.*, areas with poor infrastructure)	Price time latency risk of poor video and audio quality	Disasters remote areas	30-35000 USD Worldwide use (*i.e.*, areas with poor infrastructure)
IP-based/internet	Standard ⩾ 768 kb/s	Easy access good quality of video	Varying quality of video dependable on internet traffic	Telementoring follow-up medical education standard VC	50 USD/month - 70 Mbit line Low prices for VC equipment and line rental
ISDN	Normally 3 × 128 kb/s	Reasonably good video quality	Abandoned in the Western world in favor of 3G mobile phone and IP based telephony	Telementoring follow-up medical education	
3G mobile phone	3G mobile phone /modems	64-500 kb/s	Portable rapidly evolving new networks	No data encryption low quality on video poor lens quality Unique mobile standard not compatible with ordinary VC equipment Emergency medicine	30 USD/month for 5Gb data plan Low prices for VC equipment and carrier subscription
4G /LTE	4G mobile phones / modems	299.6 Mbit/s download and up to 75 Mbit/s upload	Varying quality of video dependable on internet traffic	Telementoring follow-up medical education standard VC	

ISDN: Integrated services digital network; VC: Video conferencing.

Figure 1 RP6 robot during laparoscopic telementoring[14].

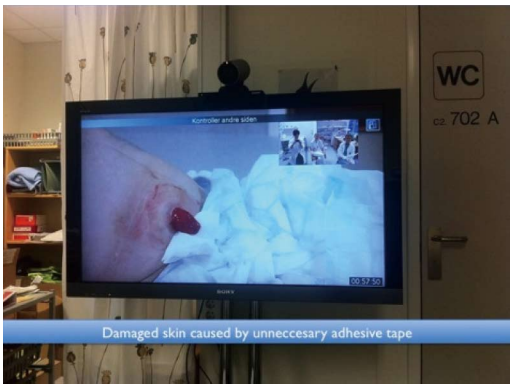

Figure 2 Stoma and post-operative wound care videoconference.

Postoperative follow-up: VC is used as an application for the follow-up of patients during the postoperative period and for outpatient consultation. In our institution, in partnership with the Norwegian Center of Integrated Care and Telemedicine, VC is being used for the follow-up of hemodialysis patients[15], dermatology and orthopedics[8,16,17].

A current RCT for stoma patients and postoperative wound problems is in progress at our institution. Stoma patients are a large and resource-demanding group with most of these patients experiencing long and time consuming travel time to and from our hospital in order to attend follow-up consultations (Figure 2). A specialized nurse is able to conduct an examination of a patient stoma whilst not being within the vicinity of the patient, then guide another nurse located within the vicinity of the patient on how to proceed with the stomas change and follow up. The visual component during the clinical examination is important to assess the stoma and post-operative wound. Early results point toward high patient compliance and satisfaction, reduced costs related to traveling are also recorded. Tele-consultation will therefore be well suited for this patient group[17,18]. We believe that an increased usage of tele-consultation and VC technology will improve the post-operative efficiency as well as reduce the costs associated to post-operative treatments for cancer patients, especially those living in rural areas that have to travel great distances to receive treatment.

TELEMENTORING IN SURGICAL EDUCATION

Telementoring uses similar technological technique of VC. Telementoring permits an expert surgeon, who remains in his/her own hospital, to instruct a non-expert from a peripheral location on how to perform a new laparoscopic technique. The application can be expanded to offer quality control with new or existing procedures[9].

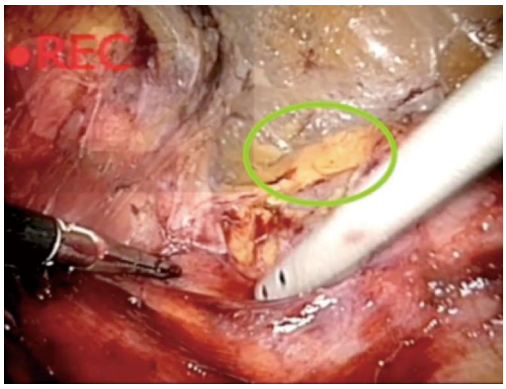

Figure 3 Visual assisted telementoring: enable the mentor to draw lines on a live laparoscopic feed.

Telementoring has been used worldwide, yet in recent years telementoring has been embraced as a viable method to enhance surgical education and has been carried over to the surgical subspecialties. Feasibility studies started in the second half of the 20th century. In the infancy of teleconferencing, Ranshaw *et al*[19] Successfully telementored a rural surgeon in more than 24 cases of laparoscopic herniorrhaphy. All of which were completed successfully. In 2003, telementoring between Brazil and the United States was performed successfully for a laparoscopic bilateral varicocelectomy and percutaneous nephrolithotomy. Over the last 15 years, several studies have shown that telementoring is possible and has positive outcomes.

Telestration technology

Mentoring a surgical resident can be conveyed at several levels: (1) Oral instructions: while watching a transmitted real-time video of the mentee surgeon operating and guiding him using only voice. This method is considered inferior since it depends on the mentor's ability to verbally deliver his instructions accurately so the mentee will understand exactly the intended action; and (2) Visual assisted mentoring: Uses a technology called telestration (Figure 3), this technology has been used mostly in weather forecasts and broadcasted sport events since the early sixties. Telestrators allow surgeons to draw a freehand sketch over the live video stream[20], which enables the mentors to convey their teaching both visually as well as verbally.

Current design limitations: Current existing telestration systems such as the one used in the Da Vinci™. Enables a remote surgeon to point on the local surgeon's display at the master console. However, it does not allow actively drawing lines that would keep their position on the live feed. Telestration however does have the capability as a teaching tool in robotic surgery, yet a proper robotic telemedicine platform does not currently exist[20].

Challenges in laparoscopic surgery training and mentoring

Laparoscopic surgery requires a high degree of special resolution, dexterity, and technical skills. An initial training period is usually required for the majority of surgeons to become expert in these complex techniques by continuous repetition of these tasks. As a result, one would anticipate that to become technically proficient at laparoscopic colorectal resections may require a much longer training period than simpler procedures such as cholecystectomy[21,22]. A number of studies have reported on the length of the learning curve by using different methods and end points over the past 20 years, resulting in suggested numbers between 11 and 110 cases[23,24]. We believe that telementoring can contribute in reducing the learning curve in complex laparoscopic surgeries, however no study has been performed so far to confirm this claim.

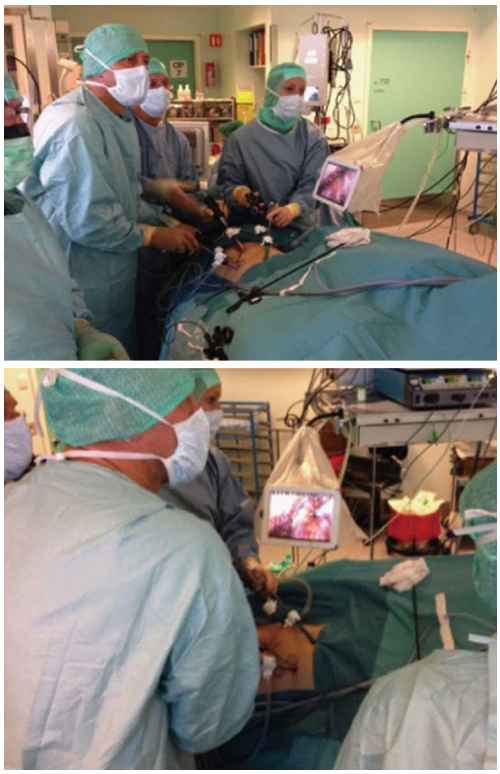

Figure 4 Tablet based mentoring in colorectal surgery at the university hospital UNN Tromsø Norway.

We have conducted several successful pilot experiments at our department with a low cost telementoring prototype based on a common home personal computer and a tablet (Figure 4), with the telementoring performed over regular internet lines. We have developed a unique software and hardware solution that allow us to capture the laparoscopic image directly from the laparoscopic camera and perform several image manipulations in real time. The software we are using provides us with a secure platform that follows and complies with the The Health Insurance Portability and Accountability Act of 1996 Privacy, Security and Breach Notification Rules and regualations(HIPAA). This unique technique is trasferable and repreducable on all laparoscopic disiplenaries *e.g.*, robotic surgery and endoscopy. So far we have con-

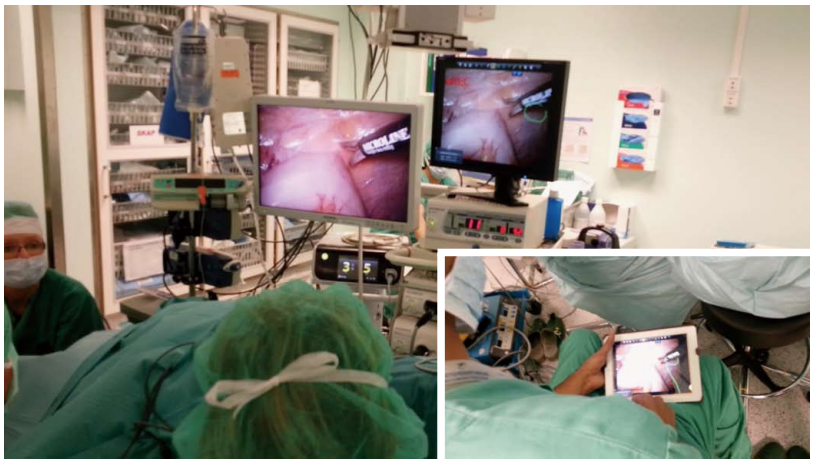

Figure 5 Onsite telementoring in the urology department at the university hospital UNN Tromsø Norway.

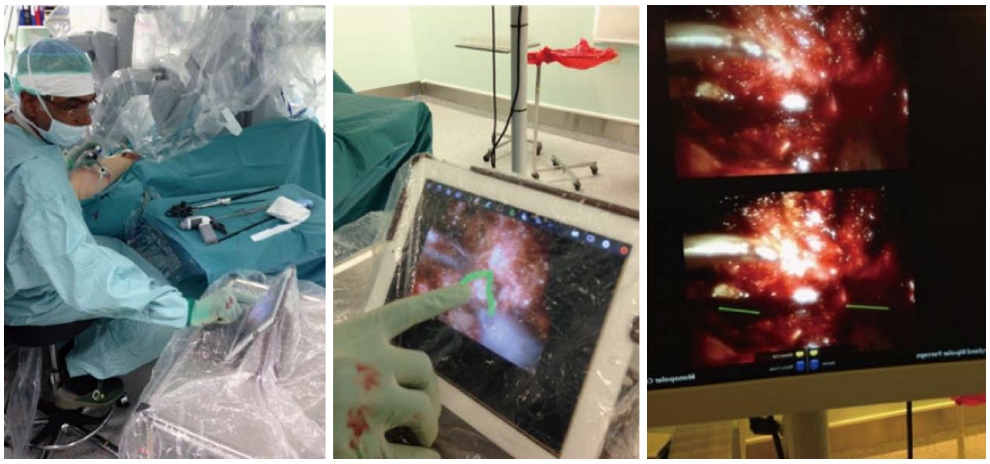

Figure 6 Robotic bedside telementoring using a unique low cost prototype.

ducted successfully in colorectal surgery: abdominoperineal resection and in urological surgery: Adrenectomy, Nephropexy,and Roboitc assisted laparoscopic prostatectomy. Three mentoring methods were used: (1) Active "hands-on" telementoring: the mentor was scrubbed and assisting in the surgery, using the tablet as a tool to enhance his verbal instructions with telestration using the tablet (Figure 4); (2) Passive/on-site mentoring-the mentor was present in the operaitng room but unscrubbed using the tablet to draw illustrations while guiding the mentee surgeons through the operation (Figure 5); and (3) Bed-side mentoring in robotic sugery: the mentor was scrubbed-in and assisting bed-side (Figure 6). All experiments were successful, we are planning in the near future off-site telementoring both short distances and transcontinental.

Telementoring limitations

Networking and Latency: Latency is defined as the amount of time it takes a packet to travel from source to destination; high latency resulted in extreme degradation of performance and has been a major setback in every live videoconferencing session. Telementoring requires a secure high-speed connection with sufficient bandwidth to provide high quality video and audio at both the mentor and mentees station. It has been shown that surgeons are generally able to compensate for delays of up to 700 ms, but delays over 500 ms (half a second) are quite noticeable and potentially detrimental[25]. Mentoring carries inherent limitations and some potential risks. The telementoring process is dependent on primarily the technological adequacy of telecommunication systems; failure of the latter may have clinical implications, which could result in operative errors and the need for conversion.

Cost of generic telementoring systems: The cost of the telementoring system, its software and complete installation (including its secure connection components), ranges from 50000 to 85000 USD. Whereas annual costs for equipment maintenance and broadband services hosting reach approximately 15000 USD[26]. Therefore installation of a telementoring system exclusively for the incorporation of advanced laparoscopic procedures within the setting of a community hospital seems rather unjustified[26]. Evidence exists for cost-effectiveness[27] and safety[28] of telementoring systems, yet there is insufficient data on educational outcomes.

Ethical and legal considerations*:* The physician-patient relationship nowadays has become challenged by

several factors, including technological evolution, novel diagnostic, and treatment modalities. Active involvement of a remote physician in surgery may disturb the therapeutic relationship with the patient and potentially challenge professional collaboration. Prior communication between treating surgeon, the remote mentor, and the patient may need to be included. Matters such as medical liability require a legal framework that would clarify the responsibilities of each part as well as the reliability of the telementoring systems and their integration in routine use. Due to the medical qualifications and licensing in different countries often not being mutually recognized, telementoring projects are currently restricted to national borders[26]. The issue of patient privacy also represents a significant concern and presents a challenge for clinical implementation of telementoring projects. We have been using a HIPPA compliant solution based on a 256-bit encryption (a VPN alternative). This encryption method is considered the best encryption standard existing for civilian medical systems and is relatively inexpensive and not as limited as a standard dedicated VPN-line.

Alternative technologies in surgical education

Virtual reality simulators: Standard surgical training has traditionally been one of apprenticeship, where the surgical trainee learns surgery under the supervision of an experienced and qualified surgeon[29]. Simulation is the replication and modeling of real-life situations for training purposes, such as testing scenario planning and design verification. "Simulation" can be any educational program or technology which removes the live patients from the equation to allow a trainee to learn and master skills in a low-stress, high-feedback environment[30]. The large range of procedures to be learned along with the different learning curves associated with the different procedures raises the problem in which a surgeon experienced in one procedure may not be experienced in another. Therefore the availability of expert surgeons for simulation training might be difficult especially in the periphery[5].

Laparoscopic surgery is different from open surgery because of complex the movements and the need for good hand-eye coordination. The fundamentals of laparoscopic surgery (FLS) box trainer is the gold standard for development of laparoscopic technical skills. However, the scoring metrics require a trained mentor and do not allow for immediate and objective feedback[31]. Virtual reality training is one of the many methods used in laparoscopic surgical training and is currently aimed at improving cognitive, psychomotor and technical skills, of both surgical residents during their studies and for maintaining overall skill of experienced surgeons[32].

Another proven advantage of surgical simulators, virtual reality (VR) simulators in specific, is a routine "warm-up" exercise before "performing" in the operating room. Despite adequate mental preparation, unlike other performers, surgeons do not routinely engage in technical "warm-up" exercises before surgery[33]. The concept of "warm-up" exercises is relatively new and is not applied as standard in today's practice[33]. Short-term practice "warm-up" for 15-20 min with tasks designed to target both psychomotor and cognitive skills that are involved in surgical procedures can greatly enhance skill proficiencies during a the follow-up procedure[34], and is shown to decrease the operative times among experienced surgeons in the operating room[35]. A recent prospective RCT done by Lendvay *et al*[36] Observed significant performance improvement and error reduction rates among surgeons of varying experience after VR warm-up for basic robotic laparoscopic surgical tasks.

Technology limitations: Learning surgical practices with an unrealistic model may lead to a negative training transfer because of the different learning abilities and limitations of the sensory, motor and cognitive system of the trainees. Another disadvantage is the initial setup cost and costs of consumables and maintenance, especially when it is not possible to simulate each and every learning task[30].

The role of computer games in surgical education and training: Minimally invasive operations provide a set of challenges that are not inherent in open operations, such as decreased tactile feedback, the fulcrum effect, and working in a 3-dimensional space while focusing on 2-dimensions. Training residents to be proficient in these specialized skills goes beyond what hands-on experience in the operating room can achieve[37].

Video games have been shown to improve hand-eye coordination, spatial visualization, manual dexterity, and rapid mental processing, which are important in the development of laparoscopic skills[38]. Middleton *et al*[38] Conducted a prospective, single-blinded RCT to determine if playing a computer game over a short duration improved VR surgical simulator performance. Their results, when compared with the control, indicated that the group playing video games significantly improved their simulator performances. Most notable findings included significantly higher scores in accuracy, time to completion, number of left-handed movements, left-handed total path length, and left-handed economy of movement for the hand-eye coordination and bimanual clipping and grasping tasks[38].

Medico-legal aspects of telementoring

The practical aspects of telementoring have not been clarified. Telementoring licensure issues are significant medico legal obstacles in the US but to a lesser degree in Europe. Telementors need to have appropriate privileges from the local hospital where the procedure is performed. During a telementored surgical procedure the primary surgeon, at the operational theatre, has primary medical authority and is the sole responsible surgeon ultimately liable for malpractice during the surgery. The premise is that the mentoring surgeon is providing only recommendations and a professional opinion[6].

CONCLUSION

Remote telementoring is more then just a real-time extension of providing surgical subspecialty advices. It allows young surgeons a safety net and builds confidence while implementing a newly learned technique. Low cost has been one of our primary goals when designing our prototypes for telementoring, in which we managed to have no significant additional expenses. Most operating rooms come replete with laparoscopic equipment, including monitors and a computer with internet capability.

The benefits of telemedicine in the areas of surgical telementoring are potentially large. Remote surgeons/mentors can facilitate procedures that would otherwise not be attempted due to complexity, difficulty, and lack of local surgeon experience. They can also give assistance when unexpected operative findings are discovered and assist in emergencies due to their previous experiences. Developed countries with remote populations such as Australia, United States (Alaska), Canada and Norway are ideal for telesurgical and telementoring technology studies.

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REVIEW

Gastrointestinal endoscopy in the pregnant woman

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Abstract

About 20000 gastrointestinal endoscopies are performed annually in America in pregnant women. Gastrointestinal endoscopy during pregnancy raises the critical issue of fetal safety in addition to patient safety. Endoscopic medications may be potentially abortifacient or teratogenic. Generally, Food and Drug Administration category B or C drugs should be used for endoscopy. Esophagogastroduodenoscopy (EGD) seems to be relatively safe for both mother and fetus based on two retrospective studies of 83 and 60 pregnant patients. The diagnostic yield is about 95% when EGD is performed for gastrointestinal bleeding. EGD indications during pregnancy include acute gastrointestinal bleeding, dysphagia > 1 wk, or endoscopic therapy. Therapeutic EGD is experimental due to scant data, but should be strongly considered for urgent indications such as active bleeding. One study of 48 sigmoidoscopies performed during pregnancy showed relatively favorable fetal outcomes, rare bad fetal outcomes, and bad outcomes linked to very sick mothers. Sigmoidoscopy should be strongly considered for strong indications, including significant acute lower gastrointestinal bleeding, chronic diarrhea, distal colonic stricture, suspected inflammatory bowel disease flare, and potential colonic malignancy. Data on colonoscopy during pregnancy are limited. One study of 20 pregnant patients showed rare poor fetal outcomes. Colonoscopy is generally experimental during pregnancy, but can be considered for strong indications: known colonic mass/stricture, active lower gastrointestinal bleeding, or colonoscopic therapy. Endoscopic retrograde cholangiopancreatography (ERCP) entails fetal risks from fetal radiation exposure. ERCP risks to mother and fetus appear to be acceptable when performed for ERCP therapy, as demonstrated by analysis of nearly 350 cases during pregnancy. Justifiable indications include symptomatic or complicated choledocholithiasis, manifested by jaundice, cholangitis, gallstone pancreatitis, or dilated choledochus. ERCP should be performed by an expert endoscopist, with informed consent about fetal radiation risks, minimizing fetal radiation exposure, and using an attending anesthesiologist. Endoscopy is likely most safe during the second trimester of pregnancy.

Key words: Gastrointestinal endoscopy; Esophagogastroduodenoscopy; Flexible sigmoidoscopy; Colonoscopy; Endoscopic retrograde cholangiopancreatography; Teratogenicity; Endoscopic indications; Endoscopy safety; Endoscopic complications; Pregnancy

Core tip: This article critically analysis the literature on the safety of gastrointestinal endoscopy during pregnancy. Endoscopy is frequently indicated during pregnancy with about 20000 endoscopies performed during pregnancy per annum in America. Although gastrointestinal endoscopy is generally safe in the non-pregnant population the safety of the fetus as well as the patient must be analyzed for endoscopy during pregnancy. This study reviews the literature on the safety of esophagogastroduodenoscopy, endoscopic retrograde cholangiopancreatography, flexible sigmoidoscopy, and colonoscopy during pregnancy and provides guidelines

about the indications, safety precautions, and efficacy of endoscopy during pregnancy.

Friedel D, Stavropoulos S, Iqbal S, Cappell MS. Gastrointestinal endoscopy in the pregnant woman. *World J Gastrointest Endosc* 2014; 6(5): 156-167 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i5/156.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i5.156

INTRODUCTION

Gastrointestinal (GI) endoscopy is a mainstay in the evaluation and treatment of GI symptoms and disorders including abdominal pain, reflux esophagitis, biliary disease, and gastrointestinal hemorrhage. It is usually considered a relatively low risk procedure in the general population that is often performed on outpatients with basic cardiopulmonary monitoring. However, there are unique considerations for endoscopy during pregnancy related to physiological alterations during pregnancy and procedural risks to the fetus in utero (Table 1). The safety of gastrointestinal endoscopy during pregnancy is important because of the commonness of GI symptoms and disorders during pregnancy. About 20000 GI endoscopies are performed annually on pregnant women in America, including > 12000 esophagogastroduodenoscopies (EGDs), > 1000 endoscopic retrograde cholangiopancreatographies (ERCPs), and several thousand sigmoidoscopies or colonoscopies[1]. About 0.4% of all endoscopies are performed during pregnancy[1-3]. The risks during pregnancy to the mother and fetus from common procedures, including upper and lower endoscopy, have not been well validated, and decisions regarding procedure performance are usually made on an individual basis based on professional society guidelines[4]. This work comprehensively, critically reviews the current data and literature on endoscopy during pregnancy; proposes recommendations on endoscopy during pregnancy based on the previously published American Society for Gastrointestinal Endoscopy (ASGE) guidelines[4], with modifications based on new data and consideration of previously unaddressed issues; analyzes how to modify procedures to promote maternal and fetal safety; recommends what to advise patients regarding fetal risks from endoscopy; and aims to stimulate new research in this field to resolve current ambiguities and controversies.

This work reviews relatively common endoscopic procedures including EGD, ERCP, flexible sigmoidoscopy, and colonoscopy, but excludes rare procedures, such as percutaneous endoscopic gastrostomy, pancreatic cyst drainage, and endoscopic therapy for achalasia, which have been recently reviewed[5].

PRE-PROCEDURE EVALUATION AND STABILIZATION

A medical history focused on the GI history, obstetric status, comorbidities, and anesthesiology risks is obtained before scheduling endoscopy during pregnancy. Endoscopy should be scheduled in consultation with an obstetrician. Patients should be medically stabilized before endoscopy, with an endpoint of relatively stable vital signs and relatively normal levels of key serum electrolytes and blood counts. In particular, patients with GI bleeding should receive volume resuscitation, including transfusion of crystalloid or packed erythrocytes as necessary, and should have severe coagulopathy corrected by transfusion of fresh frozen plasma or platelets as necessary. Relative normalization of coagulation parameters is important for successful endoscopic hemostasis.

Patients with active upper GI hemorrhage may undergo nasogastric tube lavage or administration of prokinetic agents, such as parenteral erythromycin, to clear the endoscopic field, potentially shorten procedure time, and decrease intraprocedural aspiration risks[6]. Even though no studies have focused on nasogastric tube insertion during pregnancy for GI bleeding, numerous studies have shown tolerability and safety of nasogastric tube intubation for feeding during pregnancy. These studies demonstrate that nasogastric tube intubation and feeding is generally well tolerated by the mother, with rare and mild maternal complications and with mostly favorable fetal outcomes[7]. Erythromycin is rated by the Food and Drug Administration (FDA) as a category B drug during pregnancy. No evidence of erythromycin teratogenicity was found in a study of 230 child-mother pairs exposed to erythromycin during pregnancy[8]. A large survey of Medicaid recipients in Michigan exposed to erythromycin during pregnancy found minimally or no increased rate of major congenital malformations compared to unexposed controls[9].

Patients are maintained nothing per os (npo) for several hours before EGD or ERCP to avoid intraprocedural aspiration of gastric contents. Patients with ascending cholangitis should receive antibiotic therapy to control sepsis and intravenous fluids as required for hypovolemia before ERCP. Fluid resuscitation is even more important in pregnant patients than in the general population to ensure adequate uterine/fetal perfusion during endoscopy. The patient should be positioned on the left side during endoscopy, if possible, to optimize uterine/fetal perfusion. The patient is administered supplemental oxygen by nasal cannula to optimize uterine/fetal oxygenation. Semi-elective GI endoscopy or GI surgery is optimally scheduled during the second trimester to avoid the highest risk of teratogenesis which occurs during organogenesis during the first trimester and to avoid the highest risk of inducing premature delivery which occurs during the third trimester[4]. Fetal cardiac monitoring should be considered when fetal cardiac sounds become detectable, but few cases of fetal cardiac monitoring have been reported during endoscopy and this monitoring is not considered standard of care[4].

Fetal risks from exposure to endoscopic medications, particularly anesthetics, are an important concern. Nearly 2% of pregnant women receive anesthesia without a sta-

Table 1 Unique features of endoscopy during pregnancy

1 Two or more patients at risk
2 Medications and anesthesia usually used may be contraindicated due to fetal risks
3 Patient position an issue in terms of placental blood flow
4 Greater concerns for blood pressure fluctuations due to concerns about placental perfusion
5 Greater concern for aspiration in later pregnancy
6 Disease states that may be exacerbated by pregnancy (GERD) or specific to pregnancy (hyperemesis gravidarum, gestational diabetes, third trimester liver syndromes-HELLP syndrome, *etc.*)
7 Deferral of procedure to more optimal times (*e.g.*, defer procedure from second trimester to postpartum, with possible expedited delivery)
8 Duration of procedure prime concern
9 Obstetric input and monitoring usually necessary
10 Screening for malignancy and Barrett's esophagus less of a concern
11 Avoidance of radiation-based and interventional ancillary procedures (computed tomography imaging, angiography)
12 Monopolar electrocautery (*e.g.*, with sphincterotomy) may harm fetus

GERD: Gastroesophageal reflux disease.

tistically significant correlation of worse outcomes, other than a trend towards lower neonatal birth weight[10]. The FDA classifies drugs according to fetal safety, including teratogenic and abortifacient potential as follows: Category B drugs are considered relatively safe; category C drugs are likely safe or negligibly harmful; category D drugs are potentially dangerous; and category X drugs are contraindicated during pregnancy (Table 2)[4,9,11]. Generally, category B or C drugs are selected at endoscopy during pregnancy, and category D drugs are avoided unless deemed essential and no safer alternative exists. Medications are more likely to be teratogenic when administered during the first trimester during organogenesis. Attendance of an anesthesiologist is recommended at endoscopy performed during pregnancy to optimize fetal safety of anesthetic drugs. Drugs should be administered at the lowest dosage consistent with good anesthetic practice.

Meperidine (Demerol) is generally felt to be relatively safe during pregnancy (FDA category B), but is increasingly being replaced by short acting narcotics, such as fentanyl, because of faster recovery time. Fentanyl is rated FDA category C during pregnancy. Midazolam is generally preferred over diazepam for endoscopy because it produces transient amnesia in addition to sedation. All benzodiazepines are FDA category D, but midazolam is preferred over diazepam during pregnancy because diazepam was associated with teratogenicity, especially cleft palate malformations, in several, early, small studies[12]. Recent large studies, however, have not shown this association[13,14]. Midazolam has not been associated with cleft palate abnormalities, but might have some potential for fetal injury during the first trimester[15]. Propofol is generally safe during pregnancy (FDA category B). It is generally the anesthetic agent of choice during pregnancy, provided an anesthesiologist is available for administration[4,9-11].

A woman in late pregnancy is best served by endotracheal intubation to prevent aspiration during upper endoscopy. Endotracheal intubation is often advisable during all trimesters of pregnancy for prolonged or invasive procedures, such as therapeutic ERCP, and for patients with active upper GI bleeding, particularly from esophageal varices. A consideration unique to ERCP is teratogenicity from fetal exposure in utero to intraprocedural radiation. This concern restricts ERCP to particularly strong indications, as described below. High risk endoscopies, such as therapeutic ERCP, or low risk endoscopies in high risk patients due to comorbidities or life-threatening indications for endoscopy, should ideally be performed in tertiary medical centers by expert endoscopists where an experienced team of anesthesiologists and obstetricians is available.

When obtaining consent the endoscopist should inform the patient about the potential for fetal complications even though these risks are not believed to be particularly large. The patient should be specifically apprised of fetal risks from radiation exposure if ERCP is contemplated.

Table 2 Fetal risks of endoscopic or peri-endoscopic medications used during pregnancy[1]

Medication class	FDA category of safety in pregnancy	Medications
Proton pump inhibitors	B	Lansoprazole, Pantoprazole, Dexlansoprazole, Esmeprazole, Rebeprazole
	C	Omperazole
Histamine-2 antagonists	B	Cimetidine, Famotidine, Nizatidine, Ranitidine
Antiemetics	B	Odansetron, Metoclopramide, Diphenhydramine, Trimethobenzamide, Prochloropromazine, Doxyamine Succinate and Pyridoxine
	C	Promethazine
Prokinetic agents	B	Metoclopramide, Erythromycin
Anesthesia	B	Propofol, Ketamine
Narcotics	B	Meperidine
	B	Morphine, Fentanyl
Benzodiazepines	D	Diazepam, Midazolam
Reversal agents	B	Nalozone
	C	Flumazenil
Colonic preparations	C	Polyethylene glycol, Phosphate preparations[2]
Antispasmodic	B	Glucagon

[1]FDA categorizations of drug safety during pregnancy accepted as guidelines in the current report and by the American Society for Gastrointestinal Endoscopy (ASGE[4]); [2]This review does not recommend use of phosphate preparations during pregnancy. The ASGE recommends its use "with caution"[4]. FDA: United States Food and Drug Administration.

UPPER ENDOSCOPY

EGD is the most commonly performed endoscopic procedure during pregnancy. Diagnostic EGD is useful for diagnosing gastroesophageal reflux disease (GERD), gastritis, *Helicobacter pylori* (*H. pylori*) infection, peptic ulcer disease, esophageal varices, and malignancy; whereas

Table 3 Indications for esophagogastroduodenoscopy during pregnancy

Strong indications[1]
Dysphagia > 1-2 wk, especially with diminished intake or weight loss
Odynophagia > 1-2 wk
Gross gastrointestinal hemorrhage with hematemesis and/or melena, especially if patient becomes hypotensive, requires blood products, or has a significant acute hemoglobin decline
GI hemorrhage with strong clinical suspicion of varices
Suggestion of malignancy on radiologic imaging studies (*e.g.*, MRI)
Possible gastric outlet obstruction (*e.g.*, from peptic ulcer disease)
Endoscopic therapy for continued UGI bleeding
Balloon dilatation of symptomatic UGI stricture (*e.g.*, endoscopic therapy for reflux stricture)
Moderate indications
Recurrent nausea and emesis (including possible hyperemesis gravidarum) if patient > 16-18 wk pregnant and concern exists for peptic ulcer disease with inadequate patient response to > 2 wk of conservative therapy, including PPI
Strong need for endoscopic placement of enteric tube (*e.g.*, for hyperemesis or severe, prolonged, acute pancreatitis)
Nausea and emesis after UGI surgery (including bariatric surgery) with concern for postsurgical stricture
Weak indications
Hyperemesis gravidarum during first trimester
Self-limited nausea, emesis or abdominal pain
GERD symptoms, excluding dysphagia not responsive to empiric PPI therapy
Routine endoscopic surveillance for higher risk patients (*e.g.*, EGD for personal history of familial polyposis coli)-can be deferred until postpartum
Iron deficiency anemia-should generally be deferred until postpartum

[1]These recommendations incorporate the American Society for Gastrointestinal Endoscopy (ASGE) guidelines[4] as recommendations 1-4, and 7, but the current report adds recommendations 5, 6 and 8 that were not addressed in the ASGE guidelines. MRI: Magnetic resonance imaging; UGI: Upper gastrointestinal; GERD: Gastroesophageal reflux disease; EGD: Esophagogastroduodenoscopy; PPI: Proton pump inhibitor.

therapeutic EGD is useful for hemostasis of variceal or non-variceal bleeding, dilatation of strictures, and ablation of Barrett's esophagus. Patient position, administered medications, and length of procedure are modest considerations for EGD in the general population, but become critical issues during pregnancy.

EGD appears to be relatively safe for the expectant mother and fetus, though follow-up data is limited. In a case series of 83 pregnant women undergoing EGD, 95% delivered normal infants, and the bad outcomes were uncommon and not clearly related to the EGD but were generally related to high risk pregnancies antecedent to performance of the EGD[16]. Only one maternal complication occurred after EGD: transient pyrexia 12 h after EGD with rapid defervescence without requiring antibiotic therapy and without any source of fever identified by a thorough fever work-up. In an Israeli study, only one fetus died among 60 pregnant females undergoing EGD, and no congenital abnormalities were observed in the 56 live-borne infants, excluding three voluntary abortions[17]. A mailed survey of 3300 gastroenterologists regarding 73 pregnant patients undergoing EGD yielded similarly favorable, pregnancy outcomes[18].

In the study of 83 EGDs during pregnancy, the endoscopic indications were GI hemorrhage in 45%, abdominal pain in 34%, and other in 21%. EGD was diagnostic in 95% of cases performed for acute GI bleeding during pregnancy, similar to the diagnostic yield of EGD in the general population for the same indication[16]. EGD was diagnostic in only about 60% of cases for other indications. The most common diagnosis was reflux esophagitis which occurred in 62%; this high prevalence is explained by increased acid reflux during pregnancy from increased intraabdominal pressure from the enlarged, gravid uterus and decreased LES pressure mediated by gestational hormones[19]. Mallory-Weiss tears occurred in 14%; this relatively high prevalence compared to that in nonpregnant patients is explained by the ubiquity of nausea and emesis during pregnancy. Peptic ulcer was diagnosed in only 14% of cases; this relatively low prevalence compared to that in the general population may be explained by decreased gastric acid secretion during pregnancy mediated by gestational hormones[20]. A low rate of peptic ulcer disease during pregnancy was similarly found in the Israeli study[17].

Nausea and emesis are extremely common during pregnancy. A survey reported 63% of women had nausea and emesis early in pregnancy, and 45% of women had these symptoms late in pregnancy[21]. Extreme cases, associated with paradoxical weight loss despite the pregnancy or electrolyte derangements, are called hyperemesis gravidarum. Two case series reported that endoscopic abnormalities commonly occur in pregnant patients with nausea and emesis, but diagnosis of these endoscopic abnormalities rarely altered patient management beyond instituting proton pump inhibitor therapy[16,17]. This therapy is believed to be relatively safe during pregnancy (all proton pump inhibitors but omeprazole are FDA category B, Table 2), and might reasonably be instituted empirically based on symptomatology without subjecting the patient and fetus to the risks of endoscopy. Although possibly associated with hyperemesis gravidarum, *H. pylori* infection can be reliably diagnosed noninvasively by serum antibodies or stool antigen tests[22]. EGD can therefore be typically deferred for symptoms of hyperemesis gravidarum with administration of empirical therapy comprising antiemetics and proton-pump inhibitors; EGD can be performed in the second trimester or postpartum if symptoms persist. This strategy usually obviates the need for EGD during pregnancy because symptoms of hyperemesis gravidarum typically remit after the twentieth week of pregnancy. Contrariwise, acute gross gastrointestinal hemorrhage manifested by melena, hematemesis, or hypotension, constitutes a strong indication for EGD. Patients with this indication generally have significant endoscopic findings and often require endoscopic therapy[23]. Endoscopy should also be strongly considered when upper GI malignancy is suspected, for dysphagia of recent onset persisting for $\geqslant$ 7 d, or when endoscopic therapy is anticipated (Table 3)[5,14,24].

Variceal hemorrhage is rare during pregnancy be-

cause advanced liver disease decreases fertility, but can occasionally occur in patients with underlying cirrhosis (*e.g.*, mother contracted hepatitis B in utero by vertical transmission) or from development of one of several liver failure syndromes occurring during late pregnancy, such as acute fatty liver of pregnancy. Variceal hemorrhage can, moreover, occur in noncirrhotic patients with hepatic fibrosis or portal vein obstruction because these disorders generally do not impair fertility. Pregnancy exacerbates portal hypertension mostly from gestational increases in plasma volume[25]. Almost one-third of pregnant patients with portal hypertension developed de novo varices during pregnancy, whereas about two-thirds of patients with antecedent varices experience variceal bleeding during pregnancy[26]. Patients administered beta-adrenergic receptor antagonists, such as propranolol, to prophylax against variceal bleeding should be maintained on these drugs during pregnancy. Endoscopic band ligation (EVL) is the preferred initial therapy for esophageal variceal bleeding in the general population[27], but scant published data exists concerning EVL during pregnancy, with only one published case series and about one dozen case reports[28,29]. These limited data show relatively favorable maternal and fetal outcomes of esophageal banding, compared with the poor prognosis in untreated patients[5]. Despite limited current data, endoscopic banding is considered justifiable during pregnancy. Sclerotherapy has been available for decades but is now considered a second-line therapy for variceal bleeding in the general population. The literature on sclerotherapy during pregnancy comprises < 50 patients[5,30]. The main conclusion from the limited literature is that outcomes are best for both the mother and fetus if variceal bleeding is successfully stopped by endoscopy or other interventions[31].

Data on therapeutic EGD for nonvariceal upper GI hemorrhage consist of only 4 patients, including one each of sclerotherapy for bleeding Mallory-Weiss tear, epinephrine injection for esophageal ulcer, thermocoagulation for peptic ulcer with high risk stigmata of recent hemorrhage, and electrocoagulation for duodenal ulcer with high risk stigmata of recent hemorrhage[5]. The bleeding ceased or did not recur in three patients, while the fourth patient experienced continued bleeding after endoscopic therapy that required gastric surgery. All four pregnant patients and their fetuses had favorable outcomes. This extremely limited data on therapeutic endoscopy for hemorrhage from peptic ulcers or Mallory-Weiss tears may suggest good maternal and fetal outcomes provided hemostasis is achieved[5,16]. Although considered experimental during pregnancy due to scant data, endoscopic therapy is justifiable for strong indications, including active bleeding, oozing, and nonbleeding visible vessel. This recommendation is based on expert opinion derived primarily from data on efficacy in nonpregnant patients. The current data are insufficient to recommend specific endoscopic therapies during pregnancy, among the options of banding, hemoclips, sclerotherapy, thermocoagulation, argon plasma coagulation (APC), or electrocoagulation.

Endoscopic electrocoagulation raises special concerns during pregnancy. Amniotic fluid can conduct electricity to the fetus[32]. The grounding pad should, therefore, be positioned to avoid current transmission through the uterus and fetus from the cautery device. Epinephrine is frequently injected during endoscopy to control active GI bleeding in the general population, but may decrease uterine/fetal perfusion and is rated FDA category C drug, with a weak association with teratogenesis during pregnancy[33]. This association may reflect the underlying medical condition for which the epinephrine was administered rather than intrinsic fetal toxicity[9]. Mechanical therapies, such as endoclips or bands, have a theoretical advantage for hemostasis in pregnancy because these therapies avoid fetal exposure to electricity or chemical agents.

Capsule endoscopy is generally considered contraindicated during pregnancy, as reported by the manufacturer, due to no clinical trials performed in pregnant patients[34]. Theoretically, capsule progress through bowel might be retarded in pregnant patients from bowel compression by the enlarged, gravid uterus or from anti-kinetic properties of progestin, a gestational hormone. Only a few cases of capsule endoscopy have been reported during pregnancy, including one case of bleeding from jejunal carcinoid diagnosed by capsule endoscopy and then treated surgically, with ultimate delivery of a healthy infant[35]. Although the reported cases resulted in favorable maternal and fetal outcomes, the current data are insufficient to promulgate clinical guidelines. Capsule endoscopy is currently experimental during pregnancy, but may be considered when extremely strongly indicated, especially when the alternative is gastrointestinal surgery. In providing informed consent, the physician should consider mentioning that pregnancy may theoretically increase the risk of capsule retention.

Deep enteroscopy, including single or double balloon enteroscopy, has not been reported during pregnancy. Pregnancy may theoretically render deep enteroscopy more technically challenging because of compression of bowel lumen and displacement of bowel by the enlarged, gravid uterus. Data are needed to promulgate clinical guidelines regarding safety, efficacy, and indications of deep enteroscopy during pregnancy.

LOWER ENDOSCOPY

Flexible sigmoidoscopy, a relatively simple, quick procedure, usually requires only enema preparation and minimal or no sedation and analgesia. Tap water enemas usually suffice for sigmoidoscopy[4]. Colonoscopy, however, requires more thorough colonic preparation, longer procedure times, and significant sedation and analgesia. Polyethylene glycol preparation has been reported as a preparation for colonoscopy during pregnancy but is inadequately studied in this population. Among 40 women receiving polyethylene glycol for constipation during

pregnancy, 37 had favorable fetal outcomes, and three had poor outcomes: one spontaneous abortion and two very early preterm deliveries[36]. Sodium phosphate preparations have not been studied and should not be used during pregnancy. These current recommendations are stricter than the prior ASGE recommendations to use sodium phosphate "with caution"[4], because of occasional reports of electrolyte abnormalities and even renal failure associated with administration of these preparations to dehydrated nonpregnant patients[37,38].

Despite > 6000 women having indications warranting sigmoidoscopy or colonoscopy per annum during pregnancy[39], only about sixty cases of sigmoidoscopy and only about 40 cases of colonoscopy have been reported during pregnancy[5,40]. Most procedures were performed during the second trimester. The literature likely captures a small fraction of performed procedures. In a study of 46 patients undergoing 48 sigmoidoscopies, after excluding one unknown pregnancy outcome and four voluntary abortions, 38 of the remaining 41 patients delivered healthy infants[40]. Poor pregnancy outcomes included death from prematurity of one live-borne infant, one stillbirth, and one infant with a congenital malformation. All poor outcomes occurred in high risk pregnancies and were not attributed to sigmoidoscopy. Control patients, who were matched for sigmoidoscopy indications but who did not undergo sigmoidoscopy because of the pregnancy, had similar fetal outcomes. Sigmoidoscopy during pregnancy was associated with a high diagnostic yield. Sigmoidoscopy was diagnostic in 59% of the 46 patients. It was significantly more frequently diagnostic when performed for hematochezia than for other indications [22 of 29 (76%) *vs* 5 of 17 (29%), $P < 0.03$ χ^2 test]. Sigmoidoscopic diagnoses among 29 patients with hematochezia included: de novo diagnosis or flares of IBD in 15, acute proctosigmoiditis in 3, bleeding internal hemorrhoids in 2, pseudomembranous colitis in 1, and sigmoid adenoma in 1. Among 17 patients undergoing sigmoidoscopy for other indications diagnoses included: ulcerative colitis in 2, nonspecific colitis/proctitis in 2, and postsurgical anastomotic ulcer in 1. Publication bias of reporting only dramatic cases and treatment bias of performing sigmoidoscopy only for very strong indications may have contributed to the high reported diagnostic yield. The consensus is that sigmoidoscopy is well tolerated during pregnancy with good fetal outcomes in relatively medically stable patients. Sigmoidoscopy should be strongly considered in patients with relatively strong procedure indications, including clinically significant acute lower GI bleeding, refractory chronic diarrhea of unknown etiology, distal colonic stricture, suspected IBD flare, and potential colonic malignancy.

In a study of 20 pregnant patients undergoing colonoscopy, one therapeutic colonoscopy was successfully used to decompress a colon dilated from colonic pseudoobstruction, and colonoscopy was diagnostic in 53% of the 19 remaining colonoscopies[41]. Diagnosed disorders included ulcerative colitis in 5, Crohn's colitis in 2, ischemic colitis in 2, and lymphocytic colitis in 1. Only two mothers developed clinical sequelae temporally associated with colonoscopy; they experienced hypotension which was mild and transient without further clinical sequelae. Fetal outcomes were relatively favorable: 18 healthy infants, one involuntary abortion, and 1 infant born with septum secundum congenital cardiac defect. Study patients undergoing colonoscopy, moreover, had similar or better fetal outcomes than control pregnant patients with the same indications for colonoscopy but who did not undergo colonoscopy because of the pregnancy. In another study of 8 pregnant patients undergoing colonoscopy, pregnancy outcomes included six healthy infants, one voluntary abortion, and one miscarriage four months after colonoscopy[40]. The miscarriage occurred in a mother who experienced a severe flare of ulcerative colitis after self-discontinuing her chronic immunosuppressive therapy. Similar data have been reported in about one dozen individual case reports of colonoscopy during pregnancy: a relatively high diagnostic yield of colonoscopy and a relatively low rate of poor outcomes attributable to colonoscopy[5]. As for sigmoidoscopy, the high diagnostic yield of colonoscopy may reflect publication bias and treatment bias.

Colonoscopy should generally be avoided during pregnancy and be performed only when strongly indicated. Colonoscopy should be considered for the following strong indications: evaluation of a known colonic mass or stricture detected by radiologic examination; active, clinically significant lower GI bleeding; colonoscopic decompression of colonic pseudoobstruction; or other situations to avoid colonic surgery by colonoscopic therapy. These recommendations concur with the published ASGE guidelines[4], except for adding the last two new recommendations. Colonoscopy is not all-or-none and the colonoscopist encountering technical difficulty reaching the cecum or intraprocedural patient intolerance may reasonably abort the colonoscopy without reaching the cecum. Even though the enlarged gravid uterus can compress the colonic lumen and distort normal colonic anatomy, cecal intubation is often achievable at colonoscopy during pregnancy. Reported untoward outcomes in the pregnant mother or fetus are generally related to underlying pathology, such as IBD or colon cancer, rather than the colonoscopy. When necessary, colonoscopy is preferentially performed during the second trimester[4,5,39,40]. Colonoscopy may theoretically be more teratogenic during the first trimester when organogenesis occurs and may theoretically cause more fetal injury in the third trimester by mechanical compression of the enlarged preterm uterus or by neonatal respiratory depression from colonoscopic medications administered just before labor.

Hemorrhoidal bleeding is common during advanced pregnancy because of venous pooling from increased intravascular volume and because of prolonged defecation and increased rectal pressure from increased constipation during pregnancy. Lower endoscopy may often be reasonably deferred during pregnancy for bright red blood per rectum because of this high incidence of hemorrhoidal bleeding during pregnancy and the low incidence

Table 4 Concerns about performance of endoscopic retrograde cholangiopancreatography during pregnancy

1 The procedure is technically challenging
2 The patient is normally placed in prone position for ERCP with consequently decreased placental perfusion for the significant duration of the procedure
3 The patient requires considerable anesthetic medications during ERCP due to discomfort during this particularly prolonged procedure
4 Patients often have preexisting pain and significant acute disease, such as gallstone pancreatitis or cholangitis
5 Fluoroscopy is usually required during ERCP with consequent fetal radiation exposure
6 Complications are more common in ERCP than in other endoscopic procedures and can potentially be severe (*e.g.*, pancreatitis, cholangitis, hemorrhage)
7 Sphincterotomy entails monopolar electrocautery with current possibly traversing the fetus
8 Endoscopic sphincterotomy entails risks of postsphincterotomy bleeding or perforation
9 Repeat procedures may be required, such as ERCP for retained biliary stones or stent malfunction and cholecystectomy for gallstones

ERCP: Endoscopic retrograde cholangiopancreatography.

of colon cancer in this generally relatively young female population. Colon cancer and colonic polyps, however, become a concern in older (> 40 years old) pregnant patients with chronic lower gastrointestinal bleeding[42,43]. Sigmoidoscopy can often reasonably replace colonoscopy to evaluate suspected IBD flares during pregnancy. Polypectomy can usually be deferred until after parturition for small polyps to avoid electricity traversing the fetus because such polyps are unlikely to grow much or become malignant during the interim[4]. However, medium-to-large (> 6 mm in diameter) polyps, polyps displaying high risk features such as multinodularity or central ulceration, or polyps causing lower GI bleeding should likely be removed at an index colonoscopy without deferral until postpartum. Lower endoscopy has been used several times to release an incarcerated, gravid uterus[44]. Sigmoidoscopy should be sufficient to reach this area and relieve the incarceration. Iron deficiency anemia is common during pregnancy due to physiologically increased erythropoiesis. Although colonoscopy is typically indicated to evaluate iron deficiency in the elderly, colonoscopy may generally be reasonably deferred during pregnancy until after delivery for this indication.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY AND ENDOSCOPIC ULTRASOUND

Gastroenterologists are concerned about ERCP during pregnancy (Table 4). The most common indication for ERCP during pregnancy is symptomatic choledocholithiasis, often presenting with jaundice, cholangitis, or gallstone pancreatitis. Pregnancy promotes lithogenesis due to gestational hormones. Estrogen promotes cholesterol synthesis which tends to increase cholesterol saturation of bile, and progesterone decreases gallbladder motility which tends to increase bile stasis[45]. Although cholelithiasis is estimated to have a prevalence of 3%-12% during pregnancy, only 1 per 1000 pregnancies or less are complicated by choledocholithiasis[46]. ERCP is generally the preferred therapy for choledocholithiasis to avoid complex biliary surgery for choledocholithiasis during cholecystectomy[47]. Less common ERCP indications include post-cholecystectomy bile leak, biliary strictures, or pancreatic stents for pancreatic-fluid collections. Menstruating females should be screened by urine or blood tests before ERCP to prevent accidental performance of ERCP during pregnancy with fetal exposure to ionizing radiation. For example, 3 of the 29 patients in one study undergoing ERCP during pregnancy were not known to be pregnant at the time of ERCP and were exposed to ionizing radiation without anticipation or patient discussion about potential fetal consequences[48].

The medical literature includes about 350 cases of ERCP during pregnancy. The individual studies are generally flawed due to small study size, retrospective design, failure to capture all outcomes, and limited follow-up after delivery[5,48-50]. Three retrospective series incorporating > 100 pregnant women, with almost all requiring therapeutic intervention (mostly for choledocholithiasis), imply relatively good outcomes in maternal health status, maintenance of pregnancy, and fetal outcome. These three combined studies were notable for maternal pancreatitis in 5%-16%, one spontaneous abortion 3 mo after ERCP, one fetal demise 26 h after delivery, and prematurity rate of 8%[48-50]. A retrospective study of 65 pregnant patients undergoing ERCP with sphincterotomy similarly reported favorable results[49]. There were 11 maternal complications of pancreatitis, all of which were managed medically without requiring surgery. There were no fetal deaths, perinatal deaths, or congenital malformations among the 59 known fetal outcomes[49]. In the largest prospective study, ten patients underwent biliary stenting for choledocholithiasis, biliary pancreatitis, or retained choledochal stones after cholecystectomy[51]. Cannulation was performed without sphincterotomy by using a guidewire to avoid electrocautery during pregnancy. Nine of ten patients had successful therapy, and the tenth patient underwent repeat ERCP with sphincterotomy and stent placement which was successful. All expectant mothers subsequently did well with births of healthy infants in all cases. One study of 18 patients noted no congenital abnormalities and no developmental defects detected in 11 children followed up until 11 years old[52].

A comprehensive analysis in 2011 of 296 ERCP's during pregnancy with 254 accountable pregnancy outcomes revealed (after excluding 1 voluntary abortion) healthy infants at birth in 237; premature, low-birth weight infants in 11; and bad outcomes of spontaneous abortion or infant death after live birth in 5[5]. The mother experienced post-ERCP pancreatitis in 5%-6%, and post-sphincterotomy hemorrhage in 1%, rates similar to that after ERCP with sphincterotomy in the general popula-

Table 5 Recommendations for endoscopic retrograde cholangiopancreatography during pregnancy[1]

1 Weigh conservative management and/or deferral. Radiation early in gestation is a particular concern. Second trimester may be optimal time
2 Consult with obstetrician
3 Consult with radiation physicist if feasible to calculate appropriate dosimetry
4 Obtain MRCP if useful and available
5 Employ experienced ERCP physician
6 Endoscopic ultrasound may obviate ERCP (if CBD gallstones are not extremely likely)
7 Shield fetus/Employ unit with highly collimated beam/Avoid continuous radiation
8 Employ tactics to minimize/obviate radiation: Aspirate bile/intraductal ultrasound/biliary balloon sweeps w/o fluoroscopy/cholangioscopy/biliary stent placement
9 Avoid taking hard copy radiographs of findings because these use greater amounts of radiation than fluoroscopy
10 Minimize monopolar cautery during sphincterotomy. Employ grounding pad so that electric current does not traverse uterus/fetus

[1]These current recommendations incorporate the American Society for Gastrointestinal Endoscopy (ASGE) guidelines[4] as recommendations 1,2,5, and 7-10, but the current report adds recommendations 3 and 4 that were not addressed in the ASGE guidelines. ERCP: Endoscopic retrograde cholangiopancreatography; MRCP: Magnetic resonance cholangiopancrea tography; CBD: Common bile duct.

tion[5,53]. ERCP was deemed beneficial for both mother and fetus for cases of symptomatic or complicated choledocholithiasis, manifested by jaundice, cholangitis, or pancreatitis. Caveats included that ERCP should be performed only if therapy is likely necessary and that the endoscopist should be an expert endoscopist, as technical failures resulted in relatively worse outcomes. A novice endoscopist-in-training should, therefore, not perform ERCP on a pregnant patient, even under supervision by an experienced endoscopist.

Fetal radiation exposure is a major concern for ERCP during pregnancy. Fetal risks are highest during the first trimester during organogenesis when they are considered significant at five rads of exposure[54]. Thresholds are higher and risks are lower during the second and third trimesters. Fetal radiation exposure should be estimated by fetal dosimetry, in which a detection device is placed on the abdomen over the uterus, if the anticipated dose may exceed 10 rads (100 milliGrays)[55]. Radiation exposure is usually considerably less than this amount during ERCP[56]. ERCP without fluoroscopy utilizes aspiration of bile to verify biliary cannulation, but the accuracy of this maneuver is not well validated; only a few, small, clinical series have analyzed this technique[50,57]. Other stratagems can minimize radiation exposure (Table 5), but some fluoroscopy is usually necessary. The endoscopist should minimize fluoroscopy dosage, irradiated area (small field and anterior-posterior projection), and duration by avoiding hard-copy radiographic images in favor of only fluoroscopy, utilizing a medical physicist, using a modern highly-collimated radiation unit, and employing pelvic shielding whenever possible[58].

Endoscopic spyscope (cholangioscopy) enables direct endoscopic visualization of the choledochal and pancreatic ducts. This is useful to confirm complete clearance of stones after balloon sweep or to directly examine or sample focal ductal lesions, including growths or strictures, in the general population. The safety of Spyscope technology is inadequately studied during pregnancy, with only 6 reported cases[50,59]. Although these 6 cases reported favorable maternal outcome, the ultimate fetal outcome was not reported. Direct visualization of bile ducts via cholangioscopy is appealing to confirm ductal clearance, but this maneuver may be time consuming and necessitate copious duct lavage[59]. More studies investigating fetal outcomes are needed to determine fetal safety.

Although the reported studies generally suffer from retrospective study design with only one small prospective study, relatively small numbers of study patients, lack of long term follow-up after birth, and substantial number of unknown fetal outcomes, these studies generally suggest that ERCP should be performed when strongly indicated. Strong indications for ERCP include choledocholithiasis complicated by jaundice, ascending cholangitis, or gallstone pancreatitis; and presentation with abnormal (cholestatic) liver function tests in a patient with gallstones and choledochal dilatation detected by abdominal ultrasound. These recommendations correspond with the published ASGE guidelines[4]. ERCP should not be performed for weak indications, *e.g.*, when therapy is unlikely at ERCP. In such cases MRCP is generally preferred over ERCP because of greater safety in the general population. Clinical studies of ERCP appear to show acceptable small risks to the mother that is comparable to that in the nonpregnant patient, as aforementioned for pancreatitis or post-sphincterotomy hemorrhage, and acceptable fetal risks. The benefits of stone clearance from therapeutic ERCP seem to exceed the fetal risks from performing ERCP during pregnancy. Therapeutic ERCP failed to clear choledocholithiasis in about 10% of reviewed cases. Options after therapeutic ERCP failure include repeat ERCP or surgery.

Conventional trans-abdominal ultrasound is relatively insensitive for choledocholithiasis but MRI/MRCP (magnetic resonance cholangiopancreatography) and endoscopic ultrasound (EUS) are highly accurate, radiation-free modalities to detect choledocholithiasis[60]. MRCP has a very important diagnostic role in directing management of biliary disorders in the general population, but only a couple of studies examined MRCP during pregnancy, with inadequate analysis of fetal safety. One study noted sensitivity was greatest when biliary dilation was detected on prior abdominal ultrasound[61]. In another study, MRCP was used to guide ERCP without radiation[62]. There are scant data on EUS during pregnancy, with about one dozen reported cases[50,63]. There were no maternal complications related to EUS. However, several fetal deaths were reported, which were not temporally related to the EUS and were attributed to the poor medical status of the mother at the time of undergoing EUS,

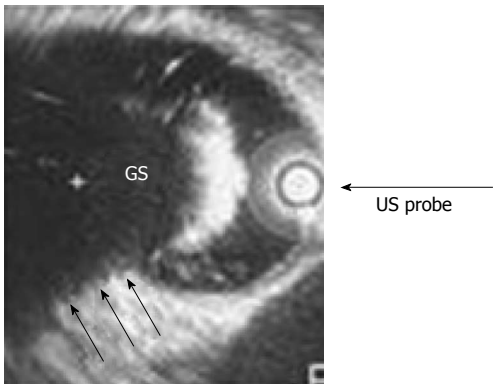

Figure 1 Intraductal ultrasound reveals a gallstone (labeled gallstone) in the common bile duct exhibiting acoustic shadowing (3 parallel arrows) in a middle-aged female patient presenting acutely with right upper quadrant pain, hyperbilirubinemia, and elevated aspartate and alanine aminotransferase levels. During pregnancy, endoscopic ultrasound provides a method to diagnose common bile duct stones without exposing the fetus to the risks of ionizing radiation from endoscopic retrograde cholangiography. US probe: Ultrasound probe; GS: Gallstone.

including recurrent cholangitis or the HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome. EUS can help gauge choledochal size and number and size of choledochal stones, but there is concern about the utility of a negative exam, especially when cholelithiasis is present. Intraductal ultrasound may be useful to verify biliary cannulation and duct clearance (Figure 1). The safety of EUS has not been validated during pregnancy, especially regarding fetal outcomes[5].

Tenets of ERCP in pregnancy include: (1) schedule ERCP expeditiously to improve patient and pregnancy outcome (*e.g.*, do not postpone indicated ERCP to second trimester of pregnancy); (2) minimize or eliminate radiation time to reduce fetal exposure; (3) achieve ductal clearance of stones or at least ensure adequate biliary drainage; and (4) facilitate cholecystectomy if necessary. Conservative management of choledocholithiasis is usually unjustified unless, perhaps, very early in pregnancy during organogenesis[64]. Various endoscopic approaches to choledocholithiasis and its complications are reported during pregnancy. Insertion of biliary stents after ductal clearance without sphincterotomy may obviate fetal risks from monopolar cautery, but the stent may become clogged and promote subsequent cholangitis[51]. Performance of both sphincterotomy and biliary stenting still mandates another ERCP that is optimally postponed until postpartum[65]. One group employed nasobiliary drainage, without fluoroscopy, in patients with severe biliary pancreatitis followed by ERCP when the patient stabilized[66].

FUTURE DIRECTIONS

In the future, the burgeoning volume of endoscopies during pregnancy may strengthen the data underlying current guidelines or help formulate modifications. Large studies, preferably prospective, with follow-up of fetal outcome are needed to determine fetal safety of endoscopy. Further data are especially needed on fetal outcome for sigmoidoscopy or colonoscopy performed during pregnancy. The scant data on therapeutic endoscopy must be augmented to determine fetal safety of various techniques of hemostasis including thermocoagulation, electrocoagulation, and APC therapy. "Best practice" recommendations may reduce controversies, such as the optimal approach to symptomatic choledocholithiasis during pregnancy. Combined cholecystectomy and ERCP has not been reported during pregnancy but might become an option[67].

Technology will be emphasized with likely sanctioned use of modalities that have been employed in pregnancy but not recommended due to insufficient data, including MRI, EUS, or capsule endoscopy. Procedures used in the general population, such as unsedated, nasal endoscopy, may be extrapolated to pregnancy. Innovations in capsule endoscopy, such as active propulsion or steering, may prevent capsule retention and thereby render it safer during pregnancy[68]. In particular, colonoscopy with sedation may be replaced by capsule endoscopy without sedation if smaller, steerable capsules are developed. Molecular genetic tests of stool or serum may obviate the need for colonoscopy to evaluate patients for rectal bleeding or colon cancer during pregnancy[69]. New colonoscopic techniques to assess polyp histology before polypectomy, such as narrow band imaging or chromoendoscopy, might help to defer polypectomy of polyps encountered at colonoscopy during pregnancy[70]. Most importantly, new technology may facilitate diagnosis and treatment in pregnancy, such as ultrasound-contrast agents for GI hemorrhage[71], mini-endoscopes, endoscopic glues for hemostasis, and novel mechanical hemostatic devices, such as endoscopic suturing[72]. The new contrast agents for MRCP should be tested in the future regarding safety during pregnancy.

Table 6 Basic principles of endoscopy during pregnancy

1 Weigh benefits of endoscopy versus conservative management
2 Defer endoscopy to second trimester or post-delivery when appropriate
3 Evaluate all proposed medications in terms of teratogenicity and abortifacient potential
4 Obtain consultation from obstetrics and preferably employ anesthesiologist
5 Position patient on left side. Avoid perturbations of blood pressure
6 Minimize drug administration and procedure time
7 For ERCP, minimize or obviate radiation (Table 5). Utilize radiation physicist and calculate dosimetry
8 Utilize bipolar electrocautery. Minimize monopolar use

ERCP: Endoscopic retrograde cholangiopancreatography.

CONCLUSION

Conservatism in performing endoscopy during pregnancy is rational. Endoscopy is usually performed when there is a strong likelihood of significant diagnostic findings and/or endoscopy therapy (*e.g.*, GI hemorrhage, IBD, compli-

cated choledocholithiasis). Patient preparation and physician adherence to general guidelines (Table 6) should help optimize outcomes. There is often multidisciplinary input from obstetricians, perinatologists, and anesthesiologists. Most pregnant women do not sustain untoward effects from endoscopy and the same seems to be the case for the fetus, although long-term follow-up data on subsequently born infants are minimal. More evidence-based guidelines and technological innovations will lessen the ambiguities and challenges in performing endoscopy during pregnancy.

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MINIREVIEWS

Update on gastric varices

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Abstract

Although less common than oesophageal variceal haemorrhage, gastric variceal bleeding remains a serious complication of portal hypertension, with a high associated mortality. In this review we provide an update on the aetiology, classification and management of gastric varices, including acute bleeding, prevention of rebleeding and primary prophylaxis. We describe the optimum management strategies for gastric varices including drug, endoscopic and radiological therapies, focusing on recent published evidence.

Key words: Varices; Gastric; Portal hypertension; Tissue glue; Transjugular intrahepatic portosystemic shunt

Core tip: Endoscopic injection of cyanoacrylate is currently the optimum, evidenced based approach to control active bleeding from gastric varices, apart from bleeding from gastro-oesophageal varice (GOV)-1 which can be treated with variceal band ligation. Transjugular intrahepatic portosystemic shunt (or balloon-occluded retrograde transvenous obliteration in experienced units) can be effective for ongoing bleeding. Cyanoacrylate or transjugular intrahepatic portosystemic shunt can prevent rebleeding from GOV-2 or isolated gastric varice, although variceal band ligation, cyanoacrylate or β-blockers can be used after bleeding from GOV-1. Non-selective β-blockers or cyanoacrylate may be used as primary prophylaxis in patients with known gastric varices, with the choice dependent on clinical and endoscopic findings.

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INTRODUCTION

Gastric varices occur in around 20% of patients with portal hypertension, mostly secondary to liver cirrhosis[1]. Although they bleed less frequently than oesophageal varices, gastric variceal bleeding tends to be more severe with a reported mortality of approximately 45%. In this review, we describe the causes, classification and management of gastric variceal bleeding.

AETIOLOGY AND RISK FACTORS

Pathogenesis of portal hypertension can be secondary to intra-hepatic (*e.g.*, cirrhosis, nodular regenerative hyperplasia), pre-hepatic (*e.g.*, portal or splenic venous obstruction) or post-hepatic (*e.g.*, hepatic venous obstruction) aetiology. Gastric varices can arise due to any of these causes of portal hypertension, but are particularly frequent in patients with splenic or portal venous obstruction.

Risk factors for gastric variceal bleeding include variceal size (large, medium and small defined as > 10 mm, 5-10 mm and < 5 mm respectively), advanced Child's grade of cirrhosis, presence of hepatocellular carcinoma, location of gastric varices (see below) and presence of red spots[1,2].

CLASSIFICATION

Gastric varices are most commonly described using Sarin's classification[1]. This system uses their location in the stomach and their relationship to oesophageal varices. It divides them into gastro-oesophageal varices (GOVs) or isolated gastric varices (IGVs). GOVs are further sub-divided into GOV-1 which extend for 2-5 cm along the lesser curve of the stomach and GOV-2 which extend beyond the gastro-oesophageal junction into the fundus of the stomach. IGVs are sub-divided into IGV-1 located in the fundus and IGV-2 located in the gastric body, antrum or pylorus (Figure 1)[1,3]. Figure 2 shows an endoscopic picture of IGV-1. Hashizume and colleagues also described a classification of gastric varices including their form, location and color, although this is less commonly used[4].

TREATMENT OF ACUTE BLEEDING

Initial management including drug therapy

Variceal haemorrhage should be suspected when a patient with known cirrhosis or evidence of portal hypertension presents with upper gastrointestinal haemorrhage. Volume restitution should be commenced immediately to maintain haemodynamic stability with blood transfusion as necessary aiming for target haemoglobin of 7-8 g/dL[5,6]. A recent Spanish randomized controlled trial showed that in Childs grade A or B cirrhotic patients with oesophageal or gastric variceal bleeding, transfusing below a threshold of 7 g/dL is safe and reduces rebleeding, need for rescue therapy and mortality[6].

Prophylactic antibiotics should be administrated early to patients with suspected or confirmed variceal bleeding as this has been shown to reduce mortality and risk of infection[7,8]. Oral quinolones are often recommended, however the antibiotic choice is often guided by local microbiological advice[5].

Vasoactive drugs should be commenced as soon as possible if variceal bleeding is suspected[5,9]. A meta-analysis comparing emergency sclerotherapy with pharmacologic treatment (including terlipressin, somatostatin or octreotide) for variceal bleeding in cirrhosis showed that vasoactive drugs are beneficial as first-line treatment[10]. However, most patients had oesophageal variceal bleeding. To date, no studies have investigated the use of vasoactive drugs specifically for gastric variceal bleeding. Early endoscopy should be undertaken to confirm the diagnosis and allow endoscopic therapy as required (see below).

Although no formal studies have assessed its use in gastric varices, the temporary use of an intra-gastric balloon such as the Sengstaken-Blackmore tube to tamponade fundal varices may be helpful if bleeding continues despite pharmacologic and endoscopic therapies. This is often used as a bridge to more definitive therapy including placement of a transjugular intrahepatic portosystemic shunt (TIPS; see below)[9,11].

Endoscopic therapies

Endoscopic treatment for gastric variceal bleeding includes endoscopic band ligation, sclerotherapy and endoscopic injection of tissue adhesives or thrombin.

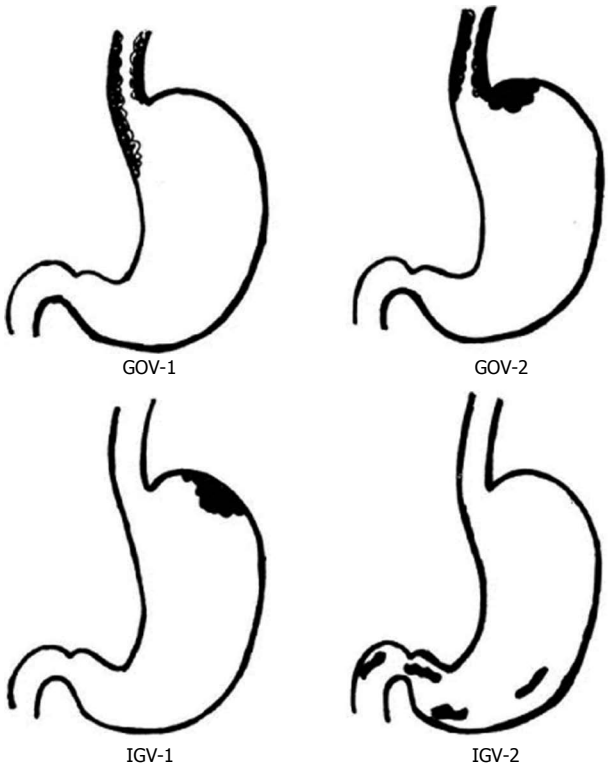

Figure 1 Classification of gastric varices. Available from Sarin *et al*[3]. GOV: Gastro-oesophageal varice; IGV: Isolated gastric varice.

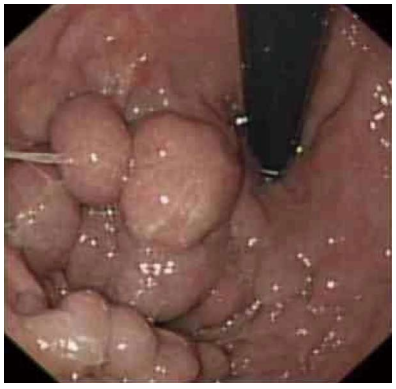

Figure 2 Endoscopic picture of isolated gastric varice-1.

Variceal band ligation: Variceal band ligation is the gold standard for the endoscopic management of oesophageal variceal haemorrhage[5,7], but its role in gastric variceal bleeding is less clear. In a prospective randomized trial by Tan *et al*[12], the efficacy of band ligation to arrest active gastric variceal bleeding in cirrhotic patients was comparable to cyanoacrylate injection, but the rebleeding rate was higher in the banding group. No difference in complications was found between the groups[12].

A study comparing variceal band ligation with the endoscopic use of detachable snares in controlling acute gastric and oesophageal variceal bleeding showed no difference between the two approaches in achieving haemo-

Table 1 Summary of larger and more recent studies using cyanoacrylate for the management of gastric variceal bleeding

Ref.	Type of study	No. of patients (follow-up)	Active bleeding	Haemostasis rate	Rebleeding rate	Complications
Cheng *et al*[19]	Case series	613 (30 mo)	23%	95%	8%	5% "major"
Kang *et al*[15]	Retrospective	127 (18 mo)	38%	98%	23%	3 % "major"
Seewald*et al*[20]	Retrospective	131 (26 mo)	63%	100%	7%	0%
Paik *et al*[14]	Retrospective	121 (12 mo)	26%	91%	13% (at 4 wk)	2% (major complications)
Kind *et al*[21]	Case series	174 (36 mo)	100%	97%	13% "late rebleeding"	8%
Ali-Al *et al*[18]	Retrospective	37 (14 mo)	86%	95%	28%	0 % "major"
Rajoriya*et al*[17]	Retrospective	31 (35 mo)	Not recorded	100%	16%	0 % "major" 6% "minor"

stasis[13]. However variceal recurrence and rebleeding rates were relatively high in both groups. Band ligation is not covered by NICE guidelines for the management of gastric variceal bleeding. However, Baveno V and AASLD guidelines suggest this type of treatment is of particular use in the endoscopic management of bleeding GOV-1, as these are generally considered extensions of oesophageal varices[5,9]. AASLD guidelines also suggest that endoscopic variceal band ligation is an option for patients who bleed from gastric fundal varices if cyanoacrylate is not available[9]. However band ligation is not of proven efficacy for non GOV-1 gastric variceal bleeding.

Sclerotherapy: A study of gastric variceal sclerotherapy with pure alcohol for acute gastric variceal bleeding reported a haemostatic rate of 66%[3]. Gastric variceal sclerotherapy appears more effective in GOV-1 than GOV-2 or IGV-1[3]. However complications associated with the procedure include fever, retrosternal and abdominal pain, dysphagia, rebleeding and ulceration. Similar to the management of oesophageal variceal bleeding, sclerotherapy has been largely replaced by band ligation when appropriate, due to the latter's lower complication and rebleeding rates.

Tissue glues: Cyanoacrylate is a monomer that undergoes rapid polymerization in presence of ionic substances including blood or tissue fluids. Tissue adhesives include histoacryl (N-butyl-cyanoacrylate) and bucrylate (isobutyl -2-cyanoacrylate) and both have been used with success for gastric varices obliteration. A standard forward viewing endoscope is used and the accessory channel and needle catheter are first flushed with lipiodol. The needle is then inserted into the gastric varix and a mixture of lipiodol and tissue adhesive is administered into the varix followed by a flush of saline or sterile water. The needle should be withdrawn immediately to prevent adherence to the varix, then flushed again with saline or sterile water. Injections can be repeated until obliteration of the varices is achieved. Obturation can be confirmed by palpation of the varices using the probe with the needle retracted.

Paik *et al*[14] retrospectively reviewed 121 patients with active or recent gastric variceal bleeding who were treated with N-butyl 2-cyanoacrylate. Bleeding control was achieved in 91% of patients with a 4-wk rebleeding rate of 13%. Fever occurred in 11% of patients and 2% had severe complications attributed to cyanoacrylate embolisms, which however resolved with conservative management. Kang *et al*[15] reported a 98% rate of haemostasis with histoacryl, with few complications. Similar to other studies, fever and abdominal pain were observed, but several uncommon complications were also reported including pulmonary embolism, splenic infarction and adrenal abscess. Case reports of thromboembolic episodes to the pulmonary cerebral and coronary circulation after tissue adhesive injection have also been described[16]. A United Kingdom study achieved an immediate haemostasis rate of 100% with endoscopic histoacryl injection in gastric variceal bleeding[17], and Al-Ali *et al*[18] reported a haemostasis rate of 95% in a Canadian population. Both studies reported no significant complications. A high haemostasis rate of 95% was also reported in a large study performed by Cheng and colleagues[19].

Current evidence of the use of tissue adhesives for gastric variceal bleeding suggests haemostasis control in > 90%. Table 1 summarizes some of the larger and most recent studies using cyanoacrylate for the treatment of gastric varices[14,15,17-21].

A randomized trial of cyanoacrylate injection *vs* TIPS for gastric variceal bleeding showed similar survival and complication rates in both groups, but TIPS was more effective in preventing rebleeding (11% *vs* 38%)[22]. Cyanoacrylate was also compared to TIPS in another two (non-randomised) studies, again with similar haemostasis rates reported between both groups[23,24].

Tissue adhesives appear to be relatively safe and effective in the management of bleeding gastric varices and are generally the endoscopic treatment of choice for bleeding from IGVs and GOV-2. They are recommended by the Baveno V, NICE and AASLD guidelines[5,7,9]. Although there are a few technical issues, appropriate training and use of a unit protocol enable most centers to use it safely and effectively.

Thrombin: Thrombin affects haemostasis by converting fibrinogen to fibrin clot and also influences platelet aggregation[25]. A standard gastroscope is used for the procedure and no specific preparation is required.

Williams *et al*[26] used bovine thrombin for control of gastric variceal bleeding and reported 100% haemostasis with no significant complications and a low rebleeding rate. Ramesh and colleagues also studied bovine thrombin in the management of bleeding gastric varices[27].

Table 2 Summary of studies using thrombin for the management of gastric variceal bleeding

Ref.	Type of thrombin used	No. of patients (follow-up)	Haemostasis	Rebleeding
Williams *et al*[26]	Bovine	11 (9 mo)	100%	27%
Przemioslo *et al*[29]	Bovine	52 (15 mo)	94%	18%
Ramesh *et al*[27]	Bovine	13 (25 mo)	92%	0%
McAvoy *et al*[28]	Human	37 (22 mo)	Not recorded	10.8%

They reported 92% haemostasis in the acute setting, with no rebleeding during follow-up. No patient had an adverse event and no technical problems were encountered. More recent studies have used human rather than bovine thrombin because of the concerns of spongiform encephalopathy.

The largest study to evaluate the efficacy of human thrombin in the management of gastric and ectopic varices bleeding suggests that human thrombin is safe and effective[28]. Thrombin is a promising therapy for bleeding gastric varices but to date no randomized data on its use are available and longer term follow-up is required, therefore more studies are required. Table 2 summarizes some of the largest and more recent studies reporting thrombin use in gastric variceal bleeding[26-29].

Radiologic therapies

Radiologic therapies for gastric varices include TIPS and BRTO (balloon-occluded retrograde transvenous obliteration).

TIPS: TIPS has been well studied in the management of oesophageal varices, with fewer studies undertaken on its use in bleeding gastric varices. An American retrospective comparative study compared TIPS with cyanoacrylate injection for gastric variceal bleeding. No differences were found in survival or rebleeding, but the group treated with TIPS had an increased morbidity requiring prolonged hospitalization because of encephalopathy[23].

Another study compared the clinical outcome of PTFE-coated stent-grafts with bare stents in patients who required emergency or elective TIPS for portal hypertension related complications[30]. During follow-up, 22% of the patients with bare stents had clinically relevant TIPS dysfunction, but no dysfunction was observed in patients treated with coated stent-grafts. Encephalopathy rates were similar. TIPS can also be used if bleeding from gastric varices is not controlled with N-butyl-cyanoacrylate injection, however the portal vein must be patent and careful patient selection is required to minimize risks of encephalopathy[7,31].

Balloon-occluded retrograde transvenous obliteration: Balloon-occluded retrograde transvenous obliteration (BRTO) is a radiologic technique used for the treatment of gastric varices. The right femoral or internal jugular vein is punctured and a balloon catheter is inserted into the left renal vein. After balloon inflation, venography is performed to identify gastric varices, gastrorenal shunts and collateral veins. The veins draining gastric varices are embolised with microcoils and a sclerosant agent is injected until all varices are obliterated.

Hong *et al*[32] compared BRTO with endoscopic injection of cyanoacrylate in the management of acute gastric variceal bleeding and high risk varices (≥ 5 mm with red spots and Child's grade B or C). The haemostasis and rebleeding rates of cyanoacrylate were 100% and 71.4% respectively compared with 76.9% and 15.4% respectively for BRTO. This was a surprising high rate of rebleeding after cyanoacrylate treatment, but included a higher proportion of patients with active bleeding than most studies. Complications were similar. The patients who rebelled were treated with rescue cyanoacrylate or BRTO. These results suggest that BRTO may have a role as rescue therapy in patients with gastric variceal bleeding.

In a small randomized study performed by Choi *et al*[33], BRTO was compared with TIPS for the urgent treatment of active gastric variceal haemorrhage. No differences were found between the groups in immediate haemostasis, rebleeding or encephalopathy. BRTO can be an alternative to TIPS for the management of acute gastric variceal bleeding if gastro-renal shunts are present[33]. However it is rarely performed outside Asian centers[34]. None of AASLD, NICE or Baveno V guidelines specifically recommend BRTO as treatment for gastric varices.

PREVENTION OF REBLEEDING (SECONDARY PROPHYLAXIS)

Therapeutic options for the prevention of gastric variceal rebleeding include use of non-selective β-blockers, repeated endoscopic injection of tissue adhesives, endoscopic band ligation (TIPS, BRTO), surgical intervention and liver transplantation.

Non selective β-blockers

A randomized controlled trial compared endoscopic cyanoacrylate injection with non-selective β-blockers in the secondary prevention of gastric variceal bleeding[35]. Patients with GOV-2 or IGV-1 were included and HVPG measurement was undertaken to assess the response to β-blockade. The cumulative two year survival rates in the cyanoacrylate and β-blocker groups were 90% and 52% respectively, with the difference linked to higher rebleeding in the β-blocker group. The median HVPG in the group treated with β-blockers fell on follow-up but rose in the cyanoacrylate group, which may be attributed to redistribution of blood flow in the portal system after variceal obturation. There was no difference in complication rates.

Another recent randomized controlled trial was reported by Hung *et al*[36] compared repeated gastric variceal obturation with or without non-selective β-blockers in patients with bleeding GOV-2 and IGV-1. The overall mortality and rebleeding rates during follow-up were similar in the two groups although adverse effects were

more common in the combination group. Therefore combining non-selective β-blockers with gastric variceal obturation does not appear to have a role in preventing GOV-2 or IGV-1 rebleeding. However the use of non-selective β-blockers may have a role in GOV-1, similar to the management of oesophageal varices[5].

Endoscopic therapies

Variceal banding: Due to the issues described above, variceal banding is generally only used as secondary prophylaxis for GOV-1 varices, but not for other types of gastric varices.

Tissue adhesives: As noted above, cyanoacrylate injection is significantly more effective than β-blocker treatment for the prevention of rebleeding from gastric varices[35] and has a lower rebleeding rate compared with band ligation in this situation[12]. As stated above, in a randomized study, rebleeding was higher in patients treated with cyanoacrylate compared with TIPS[22]. However both therapies have similar survival, and there are fewer complications with cyanoacrylate which also appears more cost-effective[22-24].

The United Kingdom study reporting long-term results of endoscopic histoacryl injection in gastric variceal bleeding reported a rebleeding rate of 16%. The mean overall follow-up was 35 mo[17]. The Canadian study, with a median follow-up period of 14 mo, reported a late rebleeding rate of 28%[18]. During a follow-up period of 30 mo, 8% of the patients in Cheng's study had recurrent bleeding[19].

Current evidence on the use of tissue adhesives for gastric variceal bleeding report re-bleeding rates of 7%-38%, with relatively few complications (Table 1).

Thrombin: Thrombin seems to be an effective and safe treatment to reduce gastric variceal rebleeding and repeated injections to achieve eradication may not be necessary[25-29]. Reported rates of rebleeding vary from 0-27% (Table 2)[26-29]. As indicated above, more studies are needed to provide comparative data with other treatment modalities before thrombin injection can be routinely used for prevention of gastric variceal rebleeding.

Radiologic therapies

TIPS: Tripathi described TIPS placement in 40 patients with gastric variceal bleeding, 232 with oesophageal, 12 with oesophageal and gastric and 8 with ectopic variceal bleeding[37]. All of the patients had portal hypertension due to parenchymal liver disease. The portal pressure gradient (PPG) before TIPS was lower in the patients with gastric variceal bleeding. Fourteen point seven percent of the patients with oesophageal varices and 20% with gastric varices rebled. Complication rates were similar. Mortality was lower in patients with gastric varices, but only if pre-TIPS PPG was ⩾ 12 mmHg. Most patients who bled after TIPS had a PPG > 7 mmHg suggesting this may be the target to protect against gastric variceal rebleeding. TIPS insertion appears effective for the prevention of gastric variceal rebleeding, although it is more invasive than endoscopic methods, has associated risks of encephalopathy and is not always available[22,30,37].

BRTO: A retrospective study performed by Jang evaluated the clinical outcomes of BRTO for the management of gastric variceal hemorrhage[38]. In 183 patents with confirmed gastric variceal bleeding, BRTO was performed with a technical success of 96.7%, and procedure-related complications occurred in 4.4%. Overall rebleeding rate was 22%.

Cho[39] evaluated clinical outcomes of BRTO in 49 patients who had gastric varices with spontaneous gastrosystemic shunts. Procedural success rate was 83.7% but there were two procedure-related deaths. Other complications included fever, ascites, pleural effusion, portal vein thrombosis, pulmonary thromboembolism and hemoglobinuria. No variceal recurrence or rebleedingwas noted. BRTO can increase PPG, secondary to increased hepatoportal flow and may aggravate pre-existing oesophageal varices and ascites[39,40]. However BRTO is a procedure that preserves hepatic function and can be used in patients with gastric varices and gastrorenal shunts if TIPS is not possible[34].

Use of EUS

The Hong Kong group suggested that patients who undergo EUS-guided cyanoacrylate injection have a significantly lower risk of recurrent bleeding from gastric varices during subsequent follow-up[41]. However others have not confirmed this[17]. There may be a role for ultrasound mini-probes in the future to assess variceal obliteration, but at present this remains an investigative technique.

A new method has been reported for the management of gastric varices with EUS which is a combination of 2-octyl-cyanoacrylate and coils[42]. Thirty patients with acute or recent bleeding from GOV-2 and IGV-1 were treated and use of coils seemed to retain cyanoacrylate with a lower volume required to obliterate varices. Haemostasis was achieved in 100% of patients with a 96% variceal obliteration rate and no procedure related complications. More studies are needed to determine the efficacy of this treatment.

Surgery

Surgical therapies include total shunts, partial (lower diameter) shunts, selective shunts and devascularization procedures. Total shunts control and prevent variceal bleeding but do not improve survival and often precipitate encephalopathy. Selective shunts have lower rates of encephalopathy and are more commonly used[43]. Eighty percent of patients have good control of bleeding and maintenance of portal perfusion with a selective distal splenorenal shunt[44]. Orloff reported that a portal-systemic shunt can be an effective therapy for bleeding varices in patients with portal vein thrombosis and preserved liver function[45]. They reported no recurrent bleeding

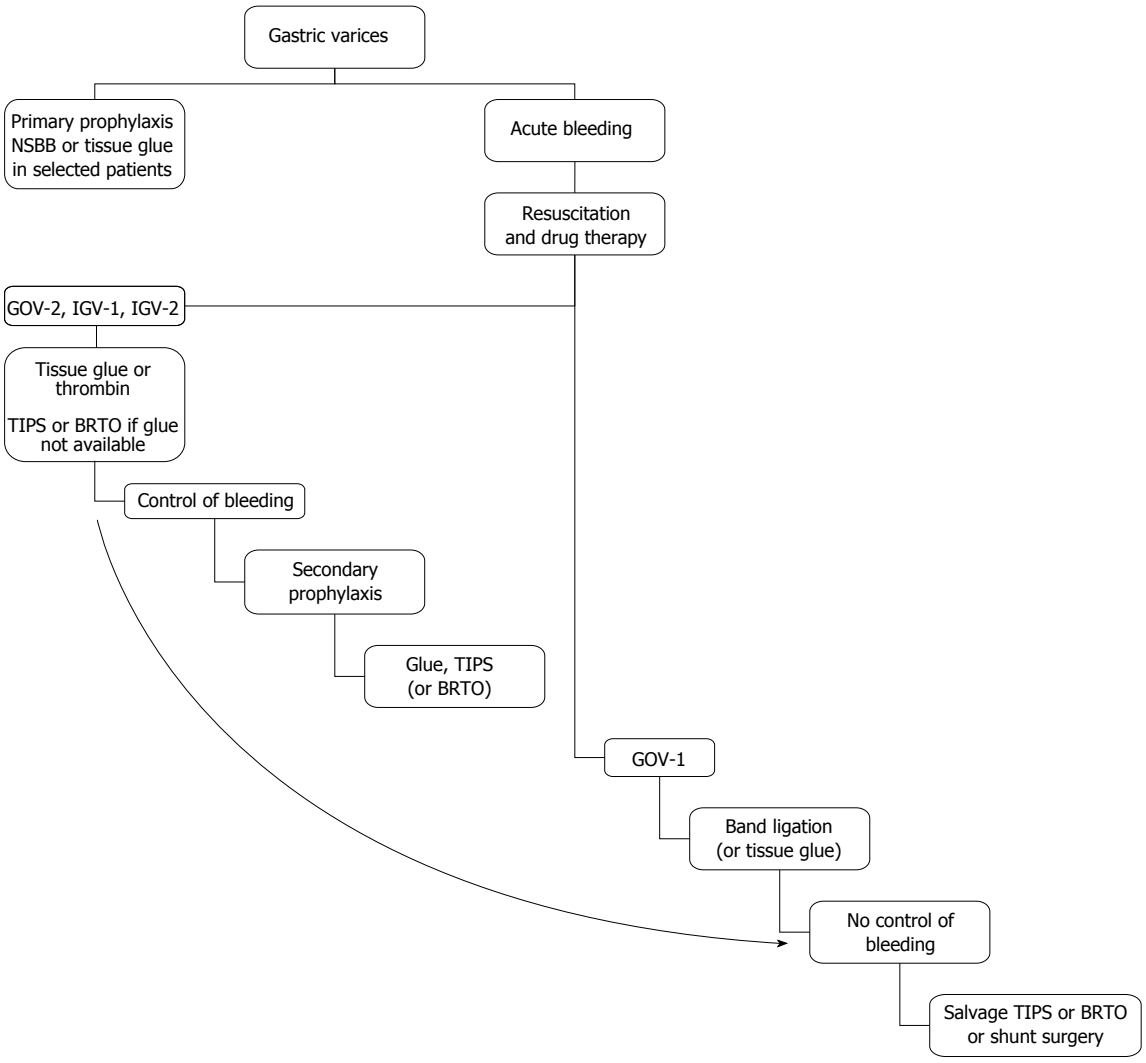

Figure 3 Suggested algorithm for treatment of gastric varices. GOV: Gastro-oesophageal varice; IGV: Isolated gastric varice; TIPS: Transjugular intrahepatic portosystemic shunt; BRTO: Balloon-occluded retrograde transvenous obliteration.

or encephalopathy and good survival rates. Splenectomy may have a role if there are IGV-1 secondary to an isolated splenic vein thrombosis[9].

Surgery for portal hypertension should be performed by experienced surgeons, in lower risk patients[43]. It is generally considered as rescue therapy, due to the associated risks and the increasing use of simpler endoscopic and radiologic procedures as described above. Liver transplantation should also be considered for eligible patients.

The Baveno V guidelines suggest use of cyanoacrylate or TIPS for the prevention of rebleeding in patients with IGV-1 and GOV-2. The AASLD guidelines consider TIPS as a treatment in patients with recurrent bleeding from fundal varices despite pharmacological and endoscopic therapy.

PRIMARY PROPHYLAXIS

A recent randomized study compared the efficacy of β-blockers, cyanoacrylate injection and no active treatment in the primary prevention of GOV-2 and IGV-1 gastric variceal bleeding[46]. Thirty eight percent, 10% and 53% of the patients bled in the β-blocker, cyanoacrylate and no-treatment groups respectively, over a median follow-up period of 26 mo. The cyanoacrylate group had significantly lower bleeding rates than the other groups for GOV-2, but not for IGV-1 patients. Mortality was significantly lower in the group treated with cyanoacrylate (7%) compared with those given no-treatment (26%) but was not significant compared with the β-blockers group (17%). β-blockers, even if HPVG fell, did not reduce the incidence of first bleeding or mortality. Therefore other factors including high variceal flow or size of gastric varices may be responsible for bleeding.

Kang *et al*[15] retrospectively analyzed patients with cirrhosis and suggested that cyanoacrylate injection is a valuable treatment for gastric varices and also an effective prophylactic treatment for high risk gastric varices.

A retrospective study by Katoh *et al*[47] evaluated the clinical outcomes of BRTO for the treatment of gastric varices. Forty-seven patients were included and it was performed as a primary prophylactic treatment in 40 patients[47]. Technique was successful in 79% with 1 and 5

year survival of 92% and 73% respectively. However this procedure is rarely performed outside Asia. Whilst relatively invasive endoscopic and radiologic procedures may have a future role in the primary prophylaxis of gastric variceal bleeding, more comparative studies are needed.

Despite the paucity of high quality studies assessing primary prophylactic therapy for gastric variceal bleeding, the Baveno V guidelines recommended that patients with gastric varices may be treated with non-selective β-blockers[5]. However these guidelines were published prior to the Indian RCT which suggested a role for cyanoacrylate in this situation[46]. The choice of therapy in this situation may well depend on variceal size, underlying liver function and other clinical factors.

CONCLUSION

Gastric variceal bleeding is a medical emergency with a high mortality. There are relatively few randomized studies assessing management of this condition, therefore guidance on therapy is based on relatively low quality data. However endoscopic injection of tissue glue or thrombin, appear effective in control of bleeding, with TIPS (or BRTO) an option if bleeding continues. To prevent rebleeding from IGV or GOV-2, cyanoacrylate or TIPS is recommended and after bleeding from GOV-1, band ligation, cyanoacrylate, or β-blockers may be used. For primary prophylaxis, patients with gastric varices may be treated with non-selective β-blockers, or possibly cyanoacrylate in selected cases. However further high quality studies are required to help clarify therapeutic strategies in this condition.

A suggested algorithm for the management of gastric varices is shown in Figure 3.

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ORIGINAL ARTICLE

Endocrine cells in the oxyntic mucosa of the stomach in patients with irritable bowel syndrome

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Abstract

AIM: To study the different endocrine cell types in the oxyntic mucosa of patients with irritable bowel syndrome (IBS).

METHODS: Seventy-six patients with IBS were included in the study (62 females and 14 males; mean age 32 years, range 18-55 years), of which 40 also fulfilled the Rome Ⅲ criteria for functional dyspepsia (FDP). Of the entire IBS cohort, 26 had diarrhea as the predominant symptom (IBS-D), 21 had a mixture of diarrhea and constipation (IBS-M), and 29 had constipation as the predominant symptom (IBS-C). Forty-three age and sex-matched healthy volunteers without any gastrointestinal complaints served as controls. The patients were asked to complete the Birmingham IBS symptom questionnaire. Both the patients and controls underwent a standard gastroscopy, during which three biopsy samples were taken from the corpus. Sections from these biopsy samples were immunostained using the avidin-biotin complex (ABC) method, for ghrelin, serotonin, somatostatin and histamine. The densities of these cell types and immunoreactivity intensities were quantified using computerized image analysis with Olympus cellSens imaging software (version 1.7).

RESULTS: The densities of the ghrelin cells in the control, IBS-total, IBS-D, IBS-M and IBS-C groups were 389 (320, 771), 359 (130, 966), 966 (529, 1154), 358 (120, 966) and 126 (0, 262) cells/mm^2, respectively. There was a significant difference between the tested groups ($P < 0.0001$). Dunn's multiple comparison test showed that the ghrelin cell density was significantly higher in IBS-D and lower in IBS-C than in the controls ($P = 0.03$ and 0.0008, respectively). The ghrelin cell density in patients with both IBS and FDP was 489 (130, 966), and in those with IBS only 490 (130, 956). There was no statistical significant difference between these 2 groups of patients ($P = 0.9$). The immunoreactivity intensity did not differ between any of the groups ($P = 0.6$). The diarrhea score of the Birmingham IBS symptom questionnaire was significantly positively correlated with ghrelin cell density ($r = 0.65$; $P < 0.0001$) and significantly inversely correlated with that of constipation ($r = 90.69$; $P < 0.0001$). The densities of the serotonin cells were 63 (51, 82), 51 (25, 115), 120 (69, 128), 74 (46, 123) and 40 (0, 46) cells/mm^2 in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively. A statistically significant difference was found between the tested groups ($P < 0.0001$). Posttest revealed that serotonin cell density was significantly higher in IBS-D and lower in IBS-C than in controls ($P = 0.02$ and 0.004, respectively), but did not differ in the IBS-total and IBS-M groups from that in controls ($P = 0.5$ and 0.4, respectively). The serotonin cell density

in patients with both IBS and FDP was 62 (25, 115) and in those with IBS only 65 (25, 123). There was no statistically significant difference between these 2 groups of patients (P = 1). The immunoreactivity intensity of serotonin did not differ significantly between any of the groups (P = 0.0.9). The serotonin cell density was significantly positively correlated with the diarrhea score of the Birmingham IBS symptom questionnaire (r = 0.56; P < 0.0001) and significantly inversely correlated with that of constipation (r = 0.51; P < 0.0001). The densities of the somatostatin cells were 97 (72, 126), 72 (0, 206), 29 (0, 80), 46 (0, 103) and 206 (194, 314) cells/mm^2 in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively (Figures 7 and 8). There was a statistically significant difference between the controls and the IBS subgroups (P < 0.0001). The density of somatostatin cells was significantly lower in the IBS-D and IBS-M groups but higher in IBS-C patients than in the controls (P < 0.01, P = 0.02, and P = 0.0008, respectively). The somatostatin cell density in patients with both IBS and FDP was 86 (0-194), and in those with IBS only 110 (0-206). There was no statistically significant difference between these 2 groups of patients (P = 0.6). There was no significant difference in somatostatin immunoreactivity intensity between the controls. The diarrhea score of the Birmingham IBS symptom questionnaire was inversely correlated with somatostatin cell density (r = 0.38; P = 0.0007) and was positively correlated with that of constipation (r = 0.64; P < 0.0001).

CONCLUSION: The finding of abnormal endocrine cells in the oxyntic mucosa shows that the endocrine cell disturbances in IBS are not restricted to the intestine. Furthermore, it appears that ghrelin, serotonin and somatostatin in the oxyntic mucosa of the stomach may play an important role in the changing stool habits in IBS through their effects on intestinal motility.

Key words: Birmingham irritable bowel syndrome symptom questionnaire; Ghrelin; Immunohistochemistry; Serotonin; Somatostatin

Core tip: There are four endocrine cell types in the oxyntic mucosa of the stomach: ghrelin, serotonin, somatostatin and histamine-containing (enterochromaffin-like) cells. These cells regulate several functions that are disturbed in patients with irritable bowel syndrome (IBS), such as motility and visceral sensation. Of all these cell types, ghrelin cells are the only endocrine cell type that has been studied in IBS patients. The present study investigated all the oxyntic mucosa endocrine cell types and reported several abnormalities that can shed light on the pathophysiology of IBS.

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INTRODUCTION

The gastrointestinal endocrine cells are scattered among the mucosal epithelial cells lining the gastrointestinal lumen[1-4]. These cells can be divided into several types according to the hormone they produce. They have specialized microvilli that project into the lumen and function as sensors of the luminal contents, and respond by releasing their hormones into the lamina propria, where they act locally (paracrine mode) or *via* the bloodstream (endocrine mode)[5-14]. These cells interact and integrate with each other, with the enteric nervous system, and with afferent and efferent nerve fibers from the autonomic nervous system[1-4]. There are four types of endocrine cell in the oxyntic mucosa of the stomach: ghrelin, serotonin, somatostatin and histamine-containing (enterochromaffin-like) cells[1,2].

Irritable bowel syndrome (IBS) is a common disorder that affects 10%-20% of the population in the Western world, producing symptoms of abdominal pain/discomfort and altered bowel habits[4]. The findings of laboratory tests, endoscopic examinations and radiological tests are normal in these patients and the diagnosis is based mainly on symptom assessment[4]. Endocrine cell abnormalities have been reported in both the small and large intestines of IBS patients[15-29], but ghrelin cells are the only endocrine cells of the oxyntic mucosa of the stomach that have been investigated thus far[30].

The aim of this study was to determine whether there are abnormalities in the densities and immunoreactivity intensities of all of the endocrine cell types in the oxyntic mucosa of the stomach in a cohort of patients with IBS, including all IBS subtypes: those with diarrhea, constipation or a mixture of both as the predominant symptom (IBS-D, IBS-C and IBS-M, respectively).

MATERIALS AND METHODS

Patients and controls

Seventy-six patients who fulfilled the Rome Ⅲ criteria for IBS were included in the study (62 females and 14 males; mean age 32 years, range 18-55 years)[31,32], of which 40 also fulfilled the Rome Ⅲ criteria for functional dyspepsia (FDP). None of the patients had used proton pump inhibitor medication in the last 6 mo. Of the entire IBS cohort, 26 had IBS-D, 21 had IBS-M, and 29 had IBS-C. All of the patients underwent a complete physical examination and were investigated by way of blood tests to exclude inflammatory, liver, endocrine and any other systemic diseases. Moreover, they were submitted to a colonoscopy with segmental biopsies, which revealed the presence of a normal terminal ileum, colon and rectum in all cases.

Forty-three age and sex-matched healthy volunteers without any gastrointestinal complaints were recruited as controls *via* local announcements at our hospitals and in the local newspapers (32 females and 11 males; mean age 40 years, range 20-58 years).

The study was approved by the Regional Committee for Medical and Health Research Ethics West, Bergen, Norway. All subjects provided both oral and written consent to participate.

Symptom assessment

The patients were asked to complete the Birmingham IBS symptom questionnaire, a disease-specific tool for assessing the symptoms of patients with IBS. Its dimensions have good reliability, external validity and sensitivity[33]. The questionnaire comprises 11 questions related to the frequencies of IBS-related symptoms. All of the questions are measured on a 5-point Likert scale. The questionnaire comprises three underlying dimensions: pain, diarrhea and constipation[33].

Gastroscopy, histopathology and immunohistochemistry

Both the patients and controls underwent a standard gastroscopy after an overnight fast, during which three biopsy samples were taken from the corpus (major curvature) and two from the antrum. The two antral biopsy samples were used in a rapid urease test for *Helicobacter pylori* (*H. pylori*) infection (HelicotecUT Plus, Strong Biotech, Taipei, Taiwan). The corpus biopsy samples were fixed overnight in 4% buffered paraformaldehyde, embedded in paraffin, and then sectioned at a thickness of 5 μm. The sections were stained with hematoxylin-eosin and immunostained using the avidin-biotin complex (ABC) method with a VECTASTAIN ABC kit and 3,3'-diaminobenzidine peroxidase substrate (DAB) as the chromogen (Vector Laboratories, Burlingame, CA, United States). The primary antibodies used were monoclonal mouse anti-N-terminus of human ghrelin (code 2016003, Millipore, Temecula, CA, United States), monoclonal mouse antihuman serotonin (clone 5HT-H209, code M0758, Dako, Glostrup, Denmark), polyclonal rabbit antisynthetic cyclic (1-14) somatostatin (code A0566, Dako), and monoclonal mouse antihistamine-hexamethylene diisocyanate-BSA (code 2273835, Millipore). The sections were incubated at room temperature for 2 h with the primary antibodies diluted to 1:200. They were then washed in phosphate-buffered saline (PBS, pH = 7.4) and incubated with biotinylated swine antimouse IgG (in the case of monoclonal antibodies) or goat antirabbit IgG (in the case of polyclonal antibodies), both diluted to 1:200, for 30 min at room temperature. After washing the slides in PBS, the sections were incubated for 30 min with peroxidase-labeled ABC diluted to 1:100, and then immersed in DAB, followed by counterstaining with hematoxylin.

Computerized image analysis

Quantification of the endocrine cells density and immunoreactivity intensity was achieved using Olympus cellSens imaging software (version 1.7). The microscope (BX 43, Olympus, Oslo, Norway) was equipped with built-in Koehler illumination for transmitted light, a light-intensity manager switch, a high-color-reproductivity LED light source, a 6-V/30-W halogen bulb and a digital camera (DP 26, Olympus). The number of immunoreactive cells, the area of epithelial cells, and the immunoreactivity intensity were measured. The number of immunoreactive cells in each field and the area of epithelium were counted manually, while the immunoreactivity intensity in each field was measured using an automatic threshold setting. A × 40 objective was used, which resulted in each frame (field) on the monitor representing a tissue area of 0.035 mm^2. Measurements were made in ten randomly chosen fields in each individual section. Immunostained sections from the IBS patients and controls were coded and mixed, and measurements were made by the same person (M.E.-S.) who was blind to the identity of the patient to whom the tissue sections belonged. The endocrine cell density is expressed as cells/mm^2 epithelium and the immunoreactivity intensity is given in arbitrary units (a.u.).

Statistical analysis

Differences in the gender distribution and the occurrence of *H. pylori* infection between the patients and controls were tested using Fisher's exact test. Differences in the age distribution were tested using the Mann-Whitney nonparametric test. Differences between the control, all IBS patients combined (IBS-total), IBS-D, IBS-M and IBS-C groups were tested using the Kruskal-Wallis nonparametric test with Dunn's posttest. Correlations were analyzed using Spearman's nonparametric test. The data are presented as median and interquartile (25^{th} and 75^{th} percentile) values and differences with $P < 0.05$ were considered statistically significant.

RESULTS

Patients and controls

The sex and age distributions did not differ significantly between the patients and controls ($P = 0.196$ and $P = 0.360$, respectively). The incidence of *H. pylori* infection did not differ between the patients ($n = 3$) and controls ($n = 2$, $P = 1.0$). The total score for the Birmingham IBS symptom questionnaire for the entire patient cohort (*i.e.*, IBS-total) was 21.5 ± 0.7. The scores on the pain, diarrhea and constipation dimensions were 7.2 ± 0.4, 6.6 ± 0.4, and 7.2 ± 0.4, respectively.

Gastroscopy, histopathology and immunohistochemistry

The esophagus was macroscopically normal while the stomach and duodenum were both macroscopically and microscopically normal in both the patients and controls. Immunoreactive cells were found in the stomach oxyntic mucosa of both the patients and controls, and were either basket or flask-shaped, sometimes with a long basal

Table 1 The densities of different endocrine cell types in controls, IBS-total, IBS-D, IBS-M and IBS-C

Endocrine cell type	Controls	IBS-total	IBS-D	IBS-M	IBS-C
Ghrelin	389 (320, 771)	359 (130, 966)	996 (529, 1154)[a]	358 (120, 966)	126 (0, 262)[c]
Serotonin	63 (51, 82)	51 (25, 115)	120 (69, 128)[a]	74 (47, 123)	40 (0, 46)[b]
Somatostatin	97 (72, 126)	72 (0, 206)	29 (0, 80)[b]	46 (0, 103)[a]	206 (194, 314)[c]

Values are expressed as median and interquartile (25th and 75th). [a]$P < 0.05$, [b]$P < 0.01$ and [c]$P < 0.0001$ *vs* controls. IBS: Irritable bowel syndrome; IBS-total: All patients with irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-M: Patients with both diarrhea and constipation; IBS-C: Patients with constipation as the predominant syndrome.

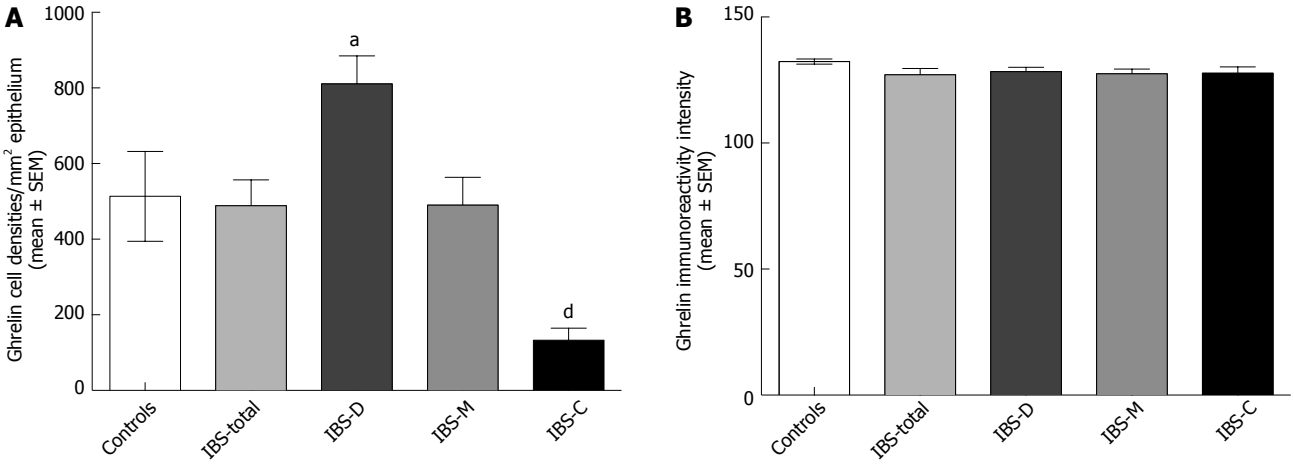

Figure 1 Ghrelin cell densities (A) and ghrelin immunoreactivity intensities (B) in the oxyntic mucosa of the stomach of controls and IBS-total, IBS-D, IBS-M and IBS-C patients. [a]$P < 0.05$, and [d]$P < 0.01$ *vs* controls. IBS: Irritable bowel syndrome; IBS-total: All patients with irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-M: Patients with both diarrhea and constipation; IBS-C: Patients with constipation as the predominant syndrome.

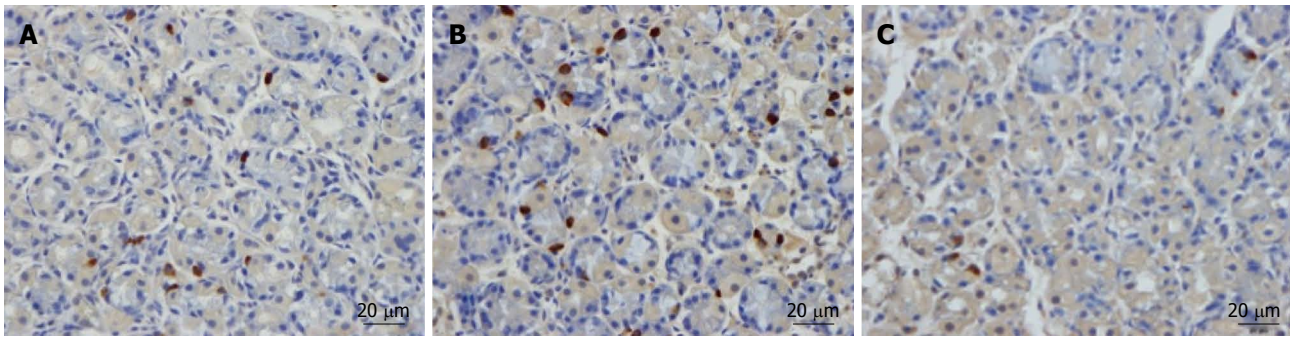

Figure 2 Ghrelin-immunoreactive cells in a control subject (A), a patient with IBS-D (B), and a patient with IBS-C (C). IBS: Irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-C: Patients with constipation as the predominant syndrome.

cytoplasmic process. There were insufficient histamine cells in the biopsy samples studied to allow any reliable quantification thereof.

Computerized image analysis

The results of the quantification of different endocrine cell types in the oxyntic mucosa of the stomach in IBS subtypes are given in Table 1.

Ghrelin: The densities of the ghrelin cells in the control, IBS-total, IBS-D, IBS-M and IBS-C groups were 389 (320, 771), 359 (130, 966), 966 (529, 1154), 358 (120, 966) and 126 (0, 262) cells/mm^2, respectively (Figures 1 and 2). The Kruskal-Wallis test revealed a statistically significant difference between the tested groups ($P < 0.0001$). Dunn's multiple comparison test showed that the ghrelin cell density was significantly higher in IBS-D and lower in IBS-C than in the controls ($P = 0.03$ and 0.0008, respectively). The ghrelin cell density in patients with both IBS and FDP was 489.0 ± 68.1, and in those with IBS only 490.1 ± 73.5. There was no statistically significant difference between these 2 groups of patients ($P = 0.9$). The immunoreactivity intensity did not differ between any of the groups, being 133 (131, 134), 131 (125, 133), 129 (125, 133), 132 (124, 134) and 130 (123, 133) a.u. in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively ($P = 0.6$). The diarrhea score of the Birmingham IBS symptom questionnaire was significantly positively

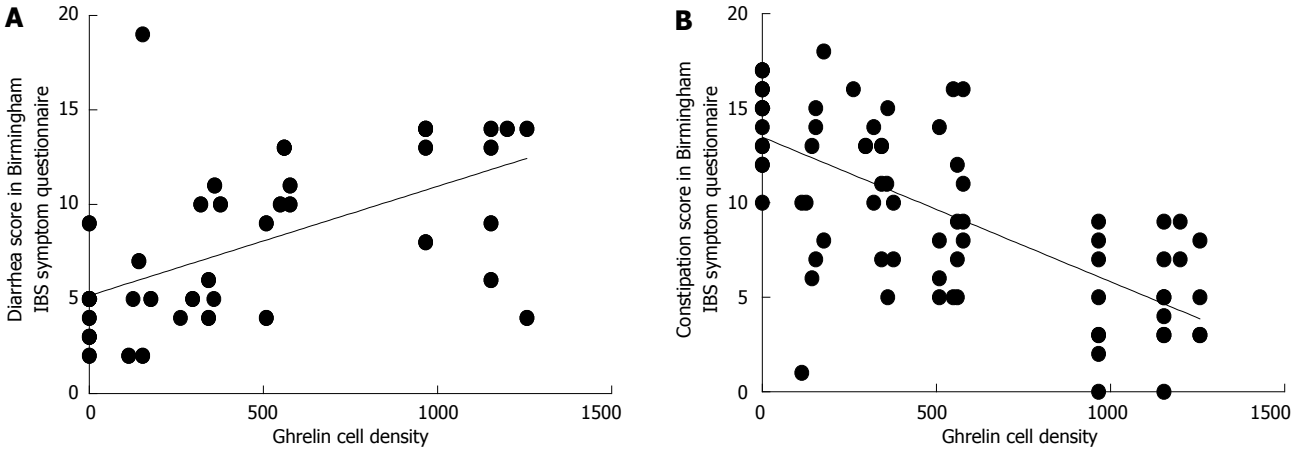

Figure 3 Correlations of ghrelin cell density with diarrhea (A) and constipation (B) scores as assessed by the Birmingham irritable bowel syndrome symptom questionnaire. IBS: Irritable bowel syndrome.

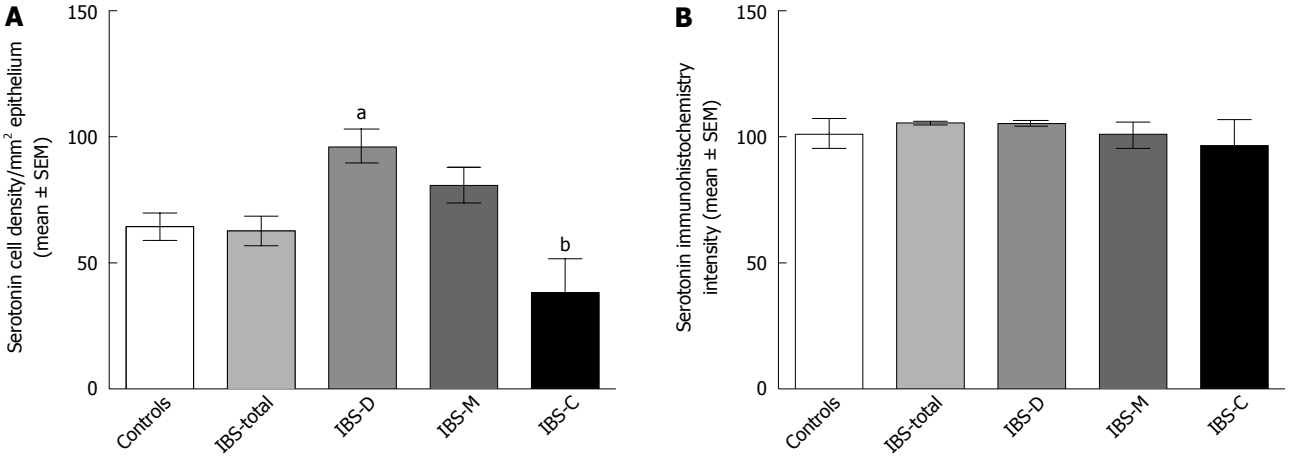

Figure 4 Serotonin cell densities (A) and serotonin immunoreactivity intensities (B) in IBS-total, IBS-D, IBS-M and IBS-C patients. [a]$P < 0.05$, [b]$P < 0.01$ *vs* controls. IBS: Irritable bowel syndrome; IBS-total: All patients with irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-M: Patients with both diarrhea and constipation; IBS-C: Patients with constipation as the predominant syndrome.

correlated with ghrelin cell density ($r = 0.65$; $P < 0.0001$) and significantly inversely correlated with that of constipation ($r = -0.69$; $P < 0.0001$; Figure 3).

Serotonin: The densities of the serotonin cells were 63 (51, 82), 51 (25, 115), 120 (69, 128), 74 (46, 123) and 40 (0, 46) cells/mm^2 in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively. The Kruskal-Wallis test revealed a statistically significant difference between the tested groups ($P < 0.0001$). Dunn's posttest revealed that serotonin cell density was significantly higher in IBS-D and lower in IBS-C than in controls ($P = 0.02$ and 0.004, respectively; Figures 4 and 5), but did not differ in the IBS-total and IBS-M groups from that in controls ($P = 0.5$ and 0.4, respectively). The serotonin cell density in patients with both IBS and FDP was 62.0 ± 6.5, and in those with IBS only 65.2 ± 9.5. There was no statistically significant difference between these 2 groups of patients ($P = 1$). The immunoreactivity intensity of serotonin did not differ significantly between any of the groups, being 107 (103, 110), 106 (103, 107), 120 (69, 128), 106 (103, 108) and 107 (101,110) a.u. in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively ($P = 0.0.9$). The serotonin cell density was significantly positively correlated with the diarrhea score of the Birmingham IBS symptom questionnaire ($r = 0.56$; $P < 0.0001$) and significantly inversely correlated with that of constipation ($r = -0.51$; $P < 0.0001$; Figure 6).

Somatostatin: The densities of the somatostatin cells were 97 (72, 126), 72 (0, 206), 29 (0, 80), 46 (0,103) and 206 (194, 314) cells/mm^2 in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively (Figures 7 and 8). The Kruskal-Wallis test indicated a statistically significant difference between the controls and the IBS subgroups ($P < 0.0001$). The density of somatostatin cells was significantly lower in the IBS-D and IBS-M groups, but higher in IBS-C patients than in the controls ($P < 0.01$, $P = 0.02$ and $P = 0.0008$, respectively). The somatostatin cell density in patients with both IBS and FDP was 86.3 ± 19.3, and in those with IBS only 110.1 ± 24.1. There was no statistical significantly difference between these 2 groups

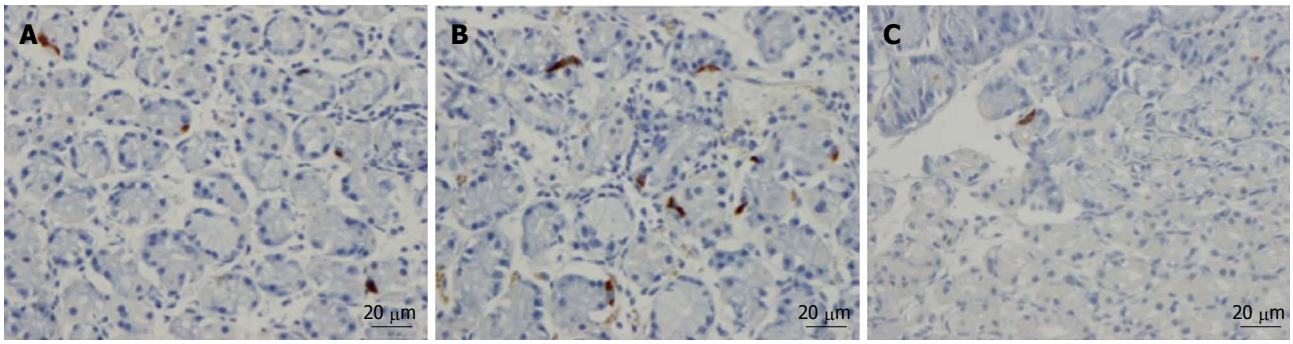

Figure 5 Serotonin cells in the oxyntic mucosa of the stomach of a control subject (A), a patient with IBS-D (B), and a patient with IBS-C (C). IBS: Irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-C: Patients with constipation as the predominant syndrome.

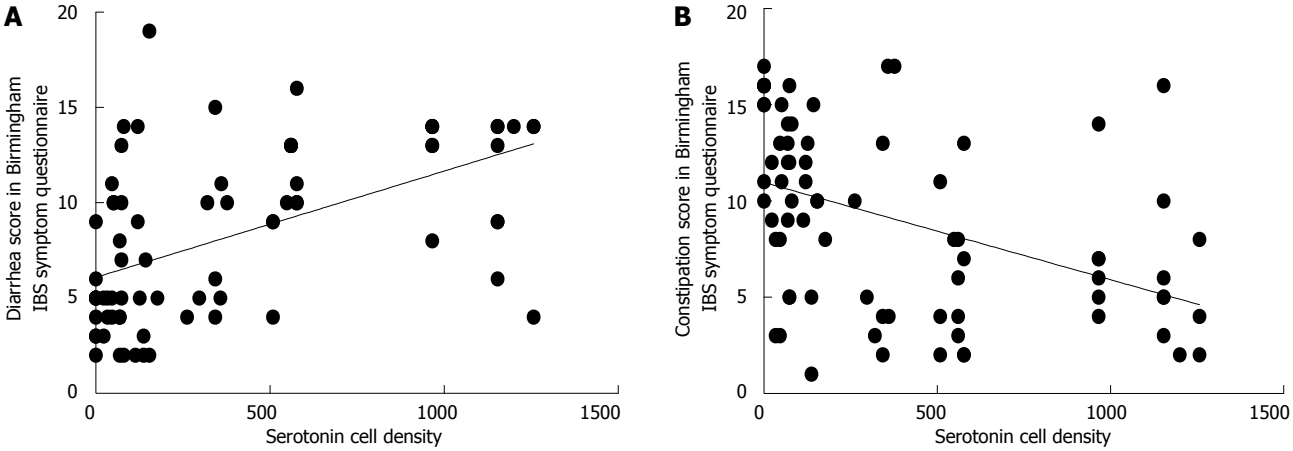

Figure 6 Correlations of serotonin cell density with diarrhea (A) and constipation (B) scores as assessed by the Birmingham irritable bowel syndrome symptom questionnaire. IBS: Irritable bowel syndrome.

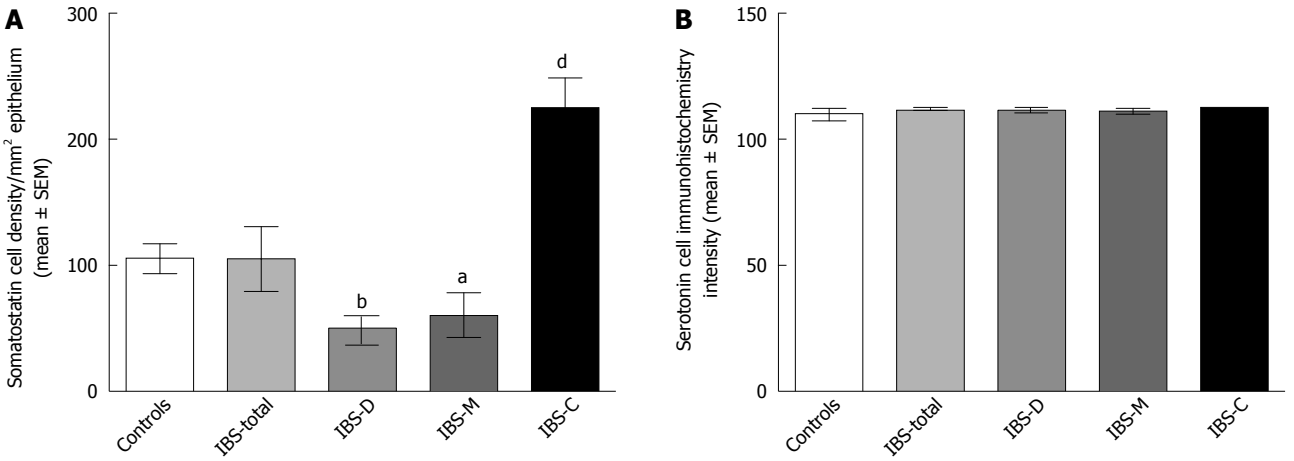

Figure 7 Somatostatin cell densities (A) and somatostatin immunoreactivity intensities (B) in IBS-total, IBS-D, IBS-M and IBS-D patients. The symbols are the same as in Figures 1 and 4. IBS: Irritable bowel syndrome; IBS-total: All patients with irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-M: Patients with both diarrhea and constipation; IBS-C: Patients with constipation as the predominant syndrome. $^{a}P < 0.05$, $^{b}P < 0.01$ and $^{d}P < 0.01$ *vs* controls.

of patients ($P = 0.6$). There was no significant difference in somatostatin immunoreactivity intensity between the controls (111; 109, 113 a.u.) and the IBS-total (112; 111, 112 a.u.), IBS-D (111; 109, 113 a.u.), IBS-M (113; 110, 113 a.u.), and IBS-C (113; 111, 113 a.u.) patients ($P = 0.9$). The diarrhea score of the Birmingham IBS symptom questionnaire was inversely correlated with somatostatin cell density ($r = -0.38$; $P = 0.0007$) and was positively correlated with that of constipation ($r = 0.64$; $P < 0.0001$; Figure 9).

DISCUSSION

The findings of the present study show that the densities

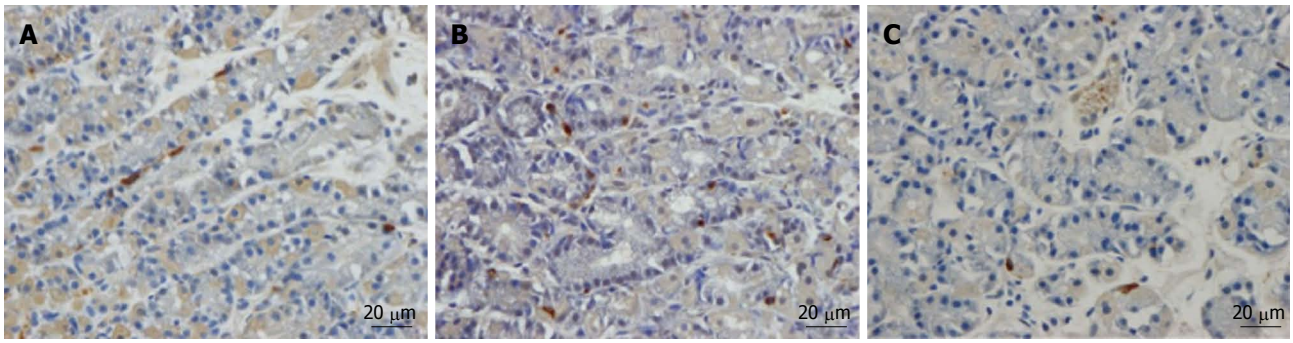

Figure 8 Somatostatin cells in the oxyntic mucosa of the stomach of a control subject (A), a patient with IBS-D (B), and a patient with IBS-C (C). IBS: Irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-C: Patients with constipation as the predominant syndrome.

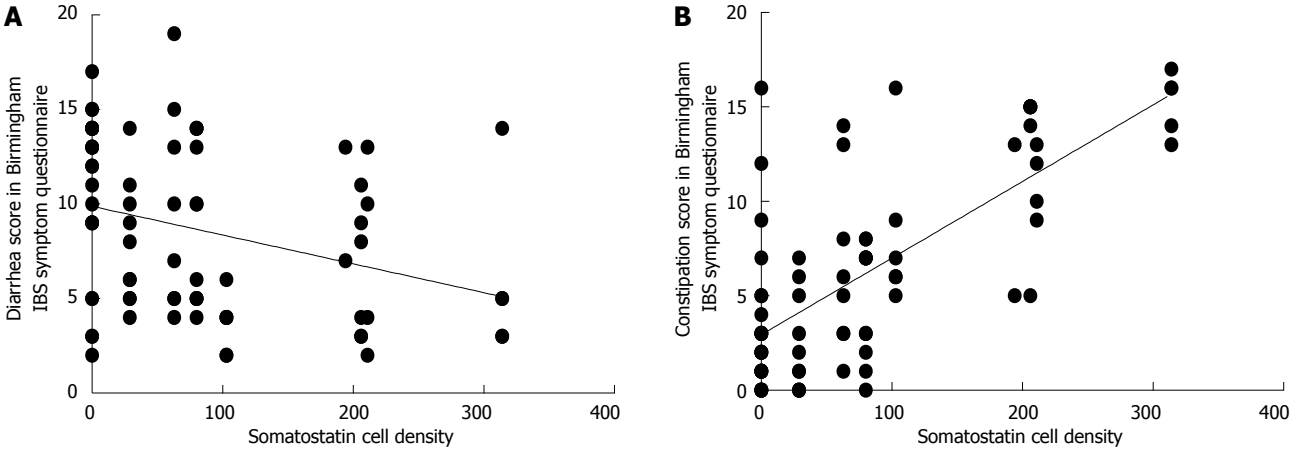

Figure 9 Correlations of somatostatin cell density with diarrhea (A) and constipation (B) scores as assessed by the Birmingham irritable bowel syndrome symptom questionnaire. IBS: Irritable bowel syndrome.

of the three main types of endocrine cells in the oxyntic mucosa of the stomach, namely ghrelin, serotonin and somatostatin cells, are abnormal in IBS patients. However, the nature of these abnormalities differ with the IBS subtype, whereby the densities of the ghrelin and serotonin cells are high in IBS-D but low in IBS-C, and the density of somatostatin cells is low in IBS-D and IBS-M but high in IBS-C. As there is no difference in the endocrine cells densities between patients with IBS/FDP and patients with IBS only, the abnormalities seen in these cells are most probably caused by IBS. The immunoreactivity intensity of ghrelin, serotonin and somatostatin in IBS patients did not differ from that of controls. This indicates that the cellular content of these hormones in IBS patients is not affected relative to controls, which is an important finding given that the cellular content of a hormone reflects its cellular synthesis and release.

Abnormalities in the endocrine cells in both the small and large intestines have been reported in patients with IBS[15-17,20-30,34,35]. In the small intestine, the duodenal cell densities of gastric inhibitory peptide (GIP), secretin, cholecystokinin (CCK) and somatostatin, and the ileal cell densities of serotonin and peptide YY (PYY) were found to be abnormal[16,18]. In the large intestine, colonic serotonin and PYY, and rectal serotonin, PYY, enteroglucagon and somatostatin cell densities have all been found to be affected[17,19,20]. Postinfectious IBS has been reported to be associated with elevated numbers of duodenal CCK cells and rectal serotonin cells, but decreased numbers of duodenal serotonin cells[15,22,24,26,29,35]. The present observation of abnormal densities of gastric endocrine cells suggests that the endocrine cell disturbances occur throughout the gastrointestinal tract of patients with IBS.

The present findings that ghrelin cell density was high in IBS-D and low in IBS-C confirm the results of an earlier study involving another cohort of IBS patients[30]. The present study also found that the ghrelin cell density was not affected in IBS-M. As well as regulating the release of growth hormone and roles in appetite and energy metabolism[36-39], ghrelin accelerates gastric and small and large intestine motility[40-51]. Ghrelin cell density was found in the present study to be strongly positively correlated with the degree of diarrhea and inversely correlated with the degree of constipation. It is thus conceivable that changes in ghrelin cell density play a role in the development of diarrhea and constipation in IBS patients.

Serotonin stimulates colonic motility and accelerates transit through the small and large intestines[52-60]. In the present study, the serotonin cell density was higher in

IBS-D and lower in IBS-C compared to healthy controls and unchanged in IBS-M. Moreover, the serotonin cell density was positively correlated with the degree of diarrhea and inversely correlated with the degree of constipation. Therefore, similar to ghrelin, serotonin seems to play a role in the development of both diarrhea and constipation in IBS patients.

Somatostatin inhibits intestinal contraction and gut exocrine and neuroendocrine secretion[2,4]. In the present study, the somatostatin cell density was low in both IBS-D and IBS-M and high in IBS-C. Furthermore, the somatostatin cell density was inversely correlated with the diarrhea score and positively correlated with the constipation score (both assessed by the Birmingham IBS symptom questionnaire). It is therefore possible that changes in the somatostatin cell density also play a considerable role in the development of both diarrhea and constipation in IBS patients.

In conclusion, the results of the present study show that the endocrine cells in the oxyntic mucosa of the stomach in IBS patients are affected and thus that the endocrine cell disturbances observed in IBS are not restricted to the intestine. Furthermore, it appears from the present findings that ghrelin, serotonin and somatostatin in the oxyntic mucosa of the stomach may play an important role in the change in stool habits in IBS *via* their effects on intestinal motility. These observations shed light on the pathophysiology of IBS and agonists and/or antagonists to the hormones described can probably be used in the near future in the treatment of patients with IBS.

COMMENTS

Background

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder. The gastrointestinal endocrine cells are localized among the mucosal epithelial cells lining the gastrointestinal lumen. There are four types of endocrine cell in the oxyntic mucosa of the stomach: ghrelin, serotonin, somatostatin and histamine-containing (enterochromaffin-like) cells. Abnormalities have been reported in both the small and large intestinal endocrine cells of IBS patients. This study was done to determine whether there are abnormalities in the endocrine cell types in the oxyntic mucosa of the stomach in patients with IBS.

Research frontiers

The present study showed for the first time that the densities of three of the four endocrine cell types occurring in the oxyntic mucosa of the stomach were abnormal in IBS patients.

Innovations and breakthroughs

The observation that the endocrine cells of oxyntic mucosa were abnormal shows that the endocrine cell disturbances in IBS are not restricted to the intestine. Hence, IBS is not a large intestine disorder. Moreover, the abnormalities observed in the oxyntic mucosa can explain the gastrointestinal dysmotility seen in IBS patients.

Applications

Based on the observations made in this study, agonists and antagonists for ghrelin, serotonin and somatostatin may be considered for the treatment of IBS.

Peer review

This is an interesting pathological study examining the density of enterochromaffin-like cells in the gastric mucosa of IBS patients. Overall, this study was a lot of work and it adds to the body of literature looking at endocrine cell contribution to the pathogenesis of IBS.

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RETROSPECTIVE STUDY

Withdrawal time in excellent or very poor bowel preparation qualities

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Abstract

AIM: To evaluate association(s) between withdrawal time and polyp detection in various bowel preparation qualities.

METHODS: Retrospective cohort analysis of screening colonoscopies performed between January 2005 and June 2011 for patients with average risk of colorectal cancer. Exclusion criteria included patients with a personal history of adenomatous polyps or colon cancer, prior colonic resection, significant family history of colorectal cancer, screening colonoscopy after other abnormal screening tests such as flexible sigmoidoscopy or barium enema, and screening colonoscopies during in-patient care. All procedures were performed or directly supervised by gastroenterologists. Main measurements were number of colonic segments with polyps and total number of colonic polyps.

RESULTS: Multivariate analysis of 8331 colonoscopies showed longer withdrawal time was associated with more colonic segments with polyps in good (adjusted OR = 1.16; 95%CI: 1.13-1.19), fair (OR = 1.13; 95%CI: 1.10-1.17), and poor (OR = 1.18; 95%CI: 1.11-1.26) bowel preparation qualities. A higher number of total polyps was associated with longer withdrawal time in good (OR = 1.15; 95%CI: 1.13-1.18), fair (OR = 1.13; 95%CI: 1.10-1.16), and poor (OR = 1.20; 95%CI: 1.13-1.29) bowel preparation qualities. Longer withdrawal time was not associated with more colonic segments with polyps or greater number of colonic polyps in bowel preparations with excellent (OR = 1.07, 95%CI: 0.99-1.26; OR = 1.11, 95%CI: 0.99-1.24, respectively) and very poor (OR = 1.02, 95%CI: 0.99-1.12; OR = 1.05, 95%CI: 0.99-1.10, respectively) qualities.

CONCLUSION: Longer withdrawal time is not associated with higher polyp number detected in colonoscopies with excellent or very poor bowel preparation quality.

Key words: Bowel preparation quality; Withdrawal time; Polyp detection; Screening colonoscopy

Core tip: This study revealed the merit of a novel finding that longer withdrawal time was not associated with higher polyp number detected in colonoscopies with excellent or very poor bowel preparation quality. The conclusion of this study may change the way we perform screening colonoscopy with excellent or very poor bowel preparation qualities, especially in those with high risk to develop complications related to prolonged sedation.

Widjaja D, Bhandari M, Loveday-Laghi V, Glandt M, Balar B. Withdrawal time in excellent or very poor bowel preparation qualities. *World J Gastrointest Endosc* 2014; 6(5): 186-192 Available from: URL: http://www.wjgnet.com/1948-5190/full/

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INTRODUCTION

Polyp detection rate during colonoscopies is influenced by factors including withdrawal time and quality of bowel preparation[1,2]. Barclay *et al*[1] reported that colonoscopies with longer withdrawal had higher adenoma detection rates. In a similar retrospective study of over 10000 colonoscopies, Simmons *et al*[3] found that prolonged withdrawal time was associated with higher polyp detection rates and that overall median polyp detection corresponded to a withdrawal time of > 6.7 min. In the same publication year, the American College of Gastroenterology and American Society for Gastrointestinal Endoscopy recommend that the average withdrawal time should exceed 6 min in normal colonoscopies in which no polypectomies or biopsies were performed[4]. The strategy of prolonged withdrawal time may logically increase polyp detection rate during colonoscopies with inadequate bowel preparation qualities, which was reported between 23% and 30% in the United States[5-9]. However, since the implementation of this recommendation, quality improvement efforts by simply mandating a minimal withdrawal time have largely proven to be unsuccessful in significantly improving polyp detection rate[10,11].

Although the effect of longer withdrawal time on higher adenoma detection rate was not related to bowel preparation quality[1], the benefit of this strategy in different bowel preparation qualities was not reported. In this study, we report association between withdrawal time and polyp detection rate in various bowel preparation qualities during screening colonoscopy in an inner city Bronx, NY, United States hospital with a high rate of inadequate bowel preparation quality.

MATERIALS AND METHODS

Study setting and patients

This study was conducted at the Bronx Lebanon Hospital Center (Bronx, NY, United States) and approved by the hospital's institutional review board. All procedures were performed or directly supervised by six full-time and two part-time gastroenterologists. We reviewed the medical records of all patients who underwent screening colonoscopies between January 1, 2005 and June 30, 2011. Data was collected through ProVationMD, an onsite computer generated medical record system used by endoscopists to create patient reports immediately after procedures. The electronic records of all these patients were reviewed for age, sex, race, date, time of colonoscopy, indication of colonoscopy, family history of colon cancer, timing of colonoscopy, bowel preparation quality, duration of colonoscope withdrawal, and polyp findings. We also collected the names of endoscopists of each case along with their average adenoma detection rates in the last 3 mo.

As per institutional practice at the time, all patients who were evaluated for screening colonoscopy were given verbal and written instructions about diet and laxative use on the day before the procedure. All these patients were instructed to consume a clear liquid diet the day before the procedure, followed by 1 gallon of polyethylene glycol (PEG) solution starting at 6 PM the evening before the procedure. In addition, 20-25 mg of bisacodyl was taken at 9 PM. Several endoscopists started giving split doses of PEG in mid-2009 for patients who underwent screening colonoscopy in the afternoon. Patients undergoing procedures before noon were not expected to take laxatives on the day of the procedure. All colonoscopies which were performed before noon were categorized as morning procedures.

Table 1 Criteria used to classify bowel preparation quality

Bowel preparation quality	Criteria
Excellent	Mucosal detail clearly visible without washing (suctioning of liquid allowed
Good	Minimal turbid fluid in colonic segments and entire mucosa well seen after cleaning
Fair	There is minor residual material in the colonic segments. Necessary to suction liquid to adequately view the colonic segments
Poor	Necessary to wash and suction to obtain a reasonable view. Portion of mucosa in colonic segments seen after cleaning but up to 15% of the mucosa not seen because of retained material
Unsatisfactory	Solid stool not cleared with washing and suctioning. More than 15% of the mucosa not seen

Based on the ProVationMD reporting system, the bowel preparation quality was rated as unsatisfactory, poor, fair, good, or excellent. Criteria for each bowel preparation quality are shown in Table 1. All patients who were included in the study had an average risk of colorectal cancer. Screening colonoscopies were performed in an outpatient setting. Patients were excluded if the indication for colonoscopy was associated with an increased risk for colorectal cancer, which included constipation, anemia, weight loss, hematemesis, hematochezia, and positive fecal occult blood test. Other exclusion criteria included patients with a personal history of adenomatous polyps or colon cancer, prior colonic resection, significant family history of colorectal cancer, screening colonoscopy after other abnormal screening tests such as flexible sigmoidoscopy or barium enema, and screening colonoscopies during in-patient care.

Variables measured

We evaluated polyp detection outcome based on the distribution and total number of colonic polyps. Distribution of the colonic polyp was defined as the number of colonic segments found to have polyps. We divided the examined intestinal portion examined during colonoscopy into eight segments: (1) rectum; (2) sigmoid colon; (3) descending colon; (4) splenic flexure; (5) transverse colon; (6) hepatic flexure; (7) ascending colon; and (8) cecum. If a polyp or several polyps were found in a colonic

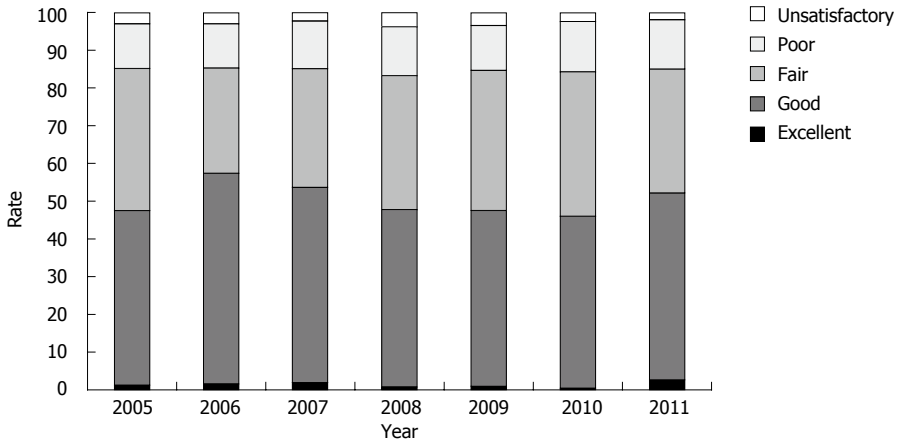

Figure 1 Distribution of bowel preparation quality for screening colonoscopies from January 1, 2005 to June 30, 2011.

segment, the colonic segment would be marked as containing polyps. Therefore, the maximum total number of colonic segments with polyps would be eight. We did not use adenoma detection rate as one of the measured outcomes, as we considered adenoma a pathologic diagnosis, not an endoscopic finding.

Statistical analysis

The data were collected and analyzed using IBM SPSS Statistics for MAC version 20. Colonoscopies without bowel preparation quality data were not included in further analysis. Bowel preparation quality was graded by the endoscopists as (1) excellent; (2) good; (3) fair; (4) poor; and (5) unsatisfactory or very poor. The five groups of bowel preparation quality were coded and classified as ordinal data. These groups were used as independent variables in the analysis. The mean duration of colonoscope withdrawal between each group of bowel preparation quality were compared by one-way ANOVA. We evaluated the differences in the number of intestinal segments with polyps and total number of colonic polyps between the five bowel preparation quality groups by Kruskal Wallis test.

Further analysis was performed to measure the correlation between polyp detection outcomes (number of colonic segments with polyps and total number of polyps) and withdrawal time using ordinal regression analysis. In this analysis, the number of intestinal segments with polyps or total number of colonic polyps was used as the dependent variable. Other variables, including withdrawal time and bowel preparation quality were included in this analysis as independent variables. Bowel preparation quality was an independent variable during subgroup analysis. Categorical data, such as race, sex, and the presence of a trainee during colonoscopy, were used as factors of independent variables. Continuous and ordinal data (*i.e.*, age, duration of colonoscope withdrawal, timing of colonoscopy, bowel preparation quality, adenoma detection rate of endoscopists, and duration of colonoscopy practice of endoscopists) were included as covariates of the independent variable. Odd ratios and 95%CI were calculated using exponents of estimates obtained from ordinal regression analysis. Statistical significance was defined as P-values ≤ 0.05.

RESULTS

During the study period, there were 8581 screening colonoscopies which fulfilled inclusion and exclusion criteria. There were 250 colonoscopies without documented information of bowel preparation quality, therefore a total of 8331 colonoscopies were used for further analysis. Of these 8331 colonoscopies, bowel preparation quality was distributed as follows: 1% was excellent, 49% were good, 35% were fair, 13% were poor, and 3% were unsatisfactory. The frequencies of bowel preparation quality for each year are shown in Figure 1. The mean age was 58.9 years (range 45-85 years), 58% were women, 24% were non-Hispanic Blacks, and 62% were Hispanic. Characteristics of the subjects based on the quality of bowel preparation are shown in Table 2.

Distribution of mean duration of colonoscope withdrawal based on bowel preparation quality is shown in Table 3. The longest mean duration of colonoscope withdrawal was seen among subjects with fair quality. Subjects with excellent bowel preparation quality had the shortest mean duration of colonoscope withdrawal.

The distribution of the number of colonic segments with polyps and total number of colonic polyps based on bowel preparation quality is shown in Table 3. The overall rate of subjects with no colonic polyps was 66% (5475/8331). The rate of patients with polyps in multiple colonic segments were 7% in the excellent group, 14% in good group, 18% in fair group, 12% in poor group, and 8% in unsatisfactory group.

Odd ratios for each variable in predicting a higher number of colonic segments with polyps and total number of polyps are shown in Table 4. Older age, male sex, longer duration of withdrawal time, bowel preparation quality and higher adenoma detection rate of endoscopist predicted a higher number of colonic segments with polyps and a higher number of polyps found during

Table 2 Patient characteristics based on bowel preparation quality *n* (%)

Characteristics	Quality of bowel preparation				
	Excellent (*n* = 108)	Good (*n* = 4051)	Fair (*n* = 2889)	Poor (*n* = 1045)	Unsatisfactory (*n* = 238)
Mean age ± SD, yr	58 ± 7.6	59 ± 7.6	59 ± 7.9	60 ± 7.7	59 ± 8.3
Women	65 (60)	2481 (61)	1596 (55)	537 (51)	117 (49)
Race					
Asian	1 (1)	32 (1)	16 (1)	4 (0)	0 (0)
White	1 (1)	47 (1)	34 (1)	15 (1)	5 (2)
Black	25 (23)	875 (22)	697 (24)	280 (27)	82 (35)
Hispanic	81 (75)	3097 (77)	2142 (74)	746 (71)	151 (63)
Morning procedure	45 (42)	1877 (46)	1212 (42)	428 (41)	78 (33)

Table 3 Withdrawal time and polyp detection based on bowel preparation quality *n* (%)

	Quality of bowel preparation					*P*-value
	Excellent (*n* = 108)	Good (*n* = 4051)	Fair (*n* = 2889)	Poor (*n* = 1045)	Unsatisfactory (*n* = 238)	
Mean duration of colonoscope withdrawal ± SD, min	10 ± 5.5	12 ± 5.3	13 ± 5.9	12 ± 5.2	11 ± 9.4	< 0.001
No. of colonic segments with polyps						< 0.001
0	85 (77)	2707 (67)	1799 (62)	703 (67)	181 (76)	
1	17 (16)	769 (19)	581 (20)	223 (21)	38 (16)	
2	3 (3)	375 (9)	305 (11)	74 (7)	13 (6)	
3	1 (1)	136 (3)	145 (5)	31 (3)	6 (3)	
4	2 (2)	43 (1)	38 (1)	11 (1)	0 (0)	
5	0 (0)	16 (0)	18 (1)	3 (0)	0 (0)	
6	0 (0)	2 (0)	3 (0)	0 (0)	0 (0)	
7	0 (0)	2 (0)	0 (0)	0 (0)	0 (0)	
8	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	
Total No. of colonic polyps						< 0.001
0	85 (77)	2707 (67)	1799 (62)	703 (67)	181 (76)	
1	13 (12)	581 (14)	446 (15)	42 (4)	30 (13)	
2	2 (2)	231 (6)	164 (6)	60 (6)	8 (3)	
3	4 (4)	256 (6)	195 (7)	37 (4)	10 (4)	
4	2 (2)	152 (4)	155 (5)	22 (2)	5 (2)	
5	1 (1)	73 (2)	90 (3)	6 (1)	4 (2)	
> 5	1 (1)	51 (1)	30 (1)	2 (0)	0 (0)	

colonoscopy. Non-Hispanic Black was a predictor for a higher number of polyps found during colonoscopy. However, the duration of colonoscopy practice of the endoscopist had an inverse relationship with the number of colonic segments with polyps and number of polyps found during colonoscopy. The mean ± SD adenoma detection rate of the endoscopist was 26% ± 8.3%. Of the colonoscopy procedures performed, 76.2% (6348/8331) of them performed by endoscopists with high adenoma detection rate, which was defined as a rate greater than 20%. In subgroup analysis, longer withdrawal time was associated with better polyp detection outcomes in patients with good, fair, or poor bowel preparation quality (Table 5). However, among those with excellent or very poor bowel preparation quality, longer duration of withdrawal time was not related to higher number of colonic segments with polyps and higher total number of colonic polyps.

DISCUSSION

Results of this study showed that half of screening colonoscopies in our minority-predominant community were performed with fair, poor, or unsatisfactory bowel preparation quality. The distribution of quality remained unchanged over the years, even though some providers started prescribing split-dose laxatives since mid-2009 for many patients undergoing afternoon screening colonoscopies. Therefore, modification of other factors, including longer withdrawal time, may improve polyp detection rate in this population.

Our study showed that the rate of colonoscopies with single colonic polyps and polyps in multiple colonic segments were highest among those with fair bowel preparation quality. In addition, this group of patients had the longest duration of colonoscope withdrawal. This likely includes patients who at presentation had poor or unsatisfactory bowel preparation quality but were cleaned in order to visualize the colon. This cleaning of intraluminal contents by diluting and suctioning has been recommended by the American Society for Gastrointestinal Endoscopy and the American College of Gastroenterology[4,12]. The rating of bowel preparation quality is to be given only after colon cleansing has taken place[12,13]. As a result of this cleansing process, the withdrawal time was prolonged.

Table 4 Predictors of higher number of colonic segments with polyps and total number of colonic polyps during screening colonoscopy

	No. colonic segment with polyps		Total No. colonic polyps	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Older age	1.01 (1.00-1.03)	0.011	1.01 (1.00-1.02)	0.026
Gender of male[1]	1.31 (1.11-1.55)	0.002	1.18 (1.00-1.39)	0.047
Race				
Asian[2]	0.89 (0.34-2.25)	NS	1.06 (0.41-2.73)	NS
White[2]	0.69 (0.33-1.45)	NS	0.70 (0.33-1.45)	NS
Black[2]	1.17 (0.97-1.41)	NS	1.22 (1.01-1.47)	0.041
Later time of colonoscopy	1.00 (1.00-1.00)	NS	1.00 (1.00-1.00)	0.043
Better bowel preparation quality	1.10 (1.00-1.21)	0.04	1.11 (1.01-1.22)	0.030
Longer duration of colonoscope withdrawal	1.14 (1.12-1.16)	< 0.0001	1.14 (1.12-1.16)	< 0.0001
Adenoma detection rate of endoscopist	1.03 (1.02-1.04)	< 0.0001	1.03 (1.02-1.04)	< 0.0001
Duration of colonoscopy practice of endoscopist	0.98 (0.97-0.98)	< 0.0001	0.98(0.97-0.99)	< 0.0001
Involvement of trainee during colonoscopy	0.93 (0.72-1.19)	NS	0.93(0.73-1.19)	NS

[1]Compared to gender of female; [2]Compared to Hispanic. NS: Not statistically significant.

Table 5 Association between longer withdrawal time and higher polyp detection in various bowel preparation qualities

	No. of colonic segments with polyps		Total No. colonic polyps	
	OR (95%CI)[1]	*P*-value	OR (95%CI)[1]	*P*-value
Excellent	1.07 (0.99-1.26)	NS	1.11 (0.99-1.24)	NS
Good	1.16 (1.13-1.19)	< 0.0001	1.15 (1.13-1.18)	< 0.0001
Fair	1.13 (1.10-1.17)	< 0.0001	1.13 (1.10-1.16)	< 0.0001
Poor	1.18 (1.11-1.26)	< 0.0001	1.20 (1.13-1.29)	< 0.0001
Unsatisfactory/very poor	1.02 (0.99-1.12)	NS	1.05 (0.99-1.10)	NS

[1]Adjusted to age, gender, race, timing of colonoscopy, endoscopist adenoma detection rate, duration of colonoscopy practice of endoscopists, involvement of trainee during colonoscopy. NS: Not statistically significant.

Multivariate analysis of our data showed that older age, male sex, longer duration of colonoscope withdrawal, bowel preparation quality, and higher endoscopist adenoma detection rate were independent predictors of higher number of colonic segments with polyps and a higher number of total polyps. Older age, male sex, and adenoma detection rate of the endoscopist were previously reported to be associated with higher polyp detection[14-17], but these factors are not modifiable during a colonoscopy procedure. On the other hand, longer duration of colonoscope withdrawal is an operator-dependent factor, which may be used as a compensatory measure when encountering inadequate bowel preparation quality. In addition, many studies have confirmed the association between this modifiable factor and adenoma detection[1,17-19].

Analysis of each bowel preparation quality group showed that longer withdrawal time was not associated with higher number of colonic segments with polyps or higher total number of colonic segments in those with excellent or unsatisfactory bowel preparation quality. These data may explain the findings of studies reporting no relationship between longer withdrawal time and polyp or adenoma detection rate. Sawhney *et al*[10] reported that the establishment of a mandatory withdrawal time of $\geqslant$ 7 min produced a significant increase in the compliance rate for withdrawal time from 65% to 100%. However, in spite of this, there was no concomitant increase in polyp detection ratio noted for all polyps (slope 0.0006; $P = 0.45$) or for 1-5 mm (slope 0.001; $P = 0.26$), 6-9 mm (slope 0.002; $P = 0.43$), or $\geqslant$ 10 mm polyps (slope 0.006; $P = 0.13$)[10]. A study by Moritz *et al*[11] also reported that withdrawal time was not associated with detection of polyps > 5 mm in size in a prospective cohort study. In addition, recording of withdrawal time or implementing a withdrawal time policy of > 7 min was not associated with a significant increase in colonic polyp detection[20]. However, all the aforementioned studies did not analyze the effect of withdrawal time based on bowel preparation qualities. It is worth pointing out that with an excellent bowel preparation quality, the completeness of evaluation might have been at a maximum that could not be improved with prolonged withdrawal time. On the other hand, prolonged withdrawal time for cleansing and evaluating the colonic mucosa of those with unsatisfactory or very poor bowel preparation is unlikely to remove solid or semi-solid stool. Therefore, aborting the procedure may be a reasonable option.

Our data showed that a longer duration of colonoscopy practice of endoscopist was inversely associated with a higher polyp detection rate. Harris *et al*[21] reported that colonoscopies in centers where over 50% of the endoscopists were of senior rank had a higher adenoma detection rate than centers with fewer senior endoscopists.

However, the senior endoscopists may have had more patients with a high risk of developing colonic polyps. In addition, the study included diagnostic procedures and colonoscopies for patients with increased risk of colonic cancer. Our finding indicates that the colonoscopy technique (*i.e.*, longer duration of colonoscope withdrawal) and better bowel preparation quality are important factors for senior endoscopists to achieve a higher polyp detection rate during screening colonoscopy in individuals with an average risk.

There are several limitations of this study, including its retrospective nature. In this study, we used overall bowel cleanliness, rather than segmental cleanliness of the bowel. The bowel preparation quality was not assessed for the right colon (cecum, ascending), mid-colon (transverse, descending), and recto-sigmoid, individually. Nonetheless, recent retrospective studies[22-25] of bowel preparation quality included the total bowel preparation scale score for the assessment. Of note, this study defined polyp detection as the number of colonic segments with polyps and number of polyps rather than adenoma detection rate of each colonoscopy. We believe that this outcome measurement reflects the overall colon condition and its endoscopic, not pathologic, lesions. Moreover, a recent study showed that the difference between benign, pre-malignant, and malignant colorectal polyps could not be accurately predicted visually alone[26]. Therefore, all polyps visualized during colonoscopy need to be excised for *ex vivo* histology regardless of size, location, or predicted pathology.

In summary, based on these data, the longest duration of colonoscope withdrawal time and highest colonic detection rate occurred in colonoscopies with fair quality. Similar to previous studies[1,10,27,28], we found that colonic segments with polyps and total number of colonic polyps are affected by colonoscopic withdrawal time. Further analysis showed that longer withdrawal time was not associated with higher polyp detection among those with an extreme spectrum of bowel preparation quality (*i.e.*, excellent and unsatisfactory/very poor). This study finds that prolonged withdrawal time in those with good, fair, and poor bowel preparation quality is likely beneficial to improving polyp detection during screening colonoscopy.

COMMENTS

Background

Many factors influence the finding of colonic polyps during colonoscopy, including clear visualization of the colonic mucosa and completeness of the examination. The presence of a significant amount of stool requiring washing and suctioning prolongs the duration of the colonoscope withdrawal. In contrast, the withdrawal time could be faster in patients with high-quality bowel preparation. The benefit of prolonged duration of colonoscope withdrawal in various degrees of bowel cleanness has not been evaluated.

Research frontiers

One study with a large number of samples found that prolonged colonoscope withdrawal time was associated with higher polyp detection rates and that the overall median polyp detection corresponded to a withdrawal time of > 6.7 min. Based on this study, United States gastroenterology societies recommend that the average colonoscope withdrawal time should exceed 6 min, not including time spent for removal of the polyps. However, since the implementation of this recommendation, quality improvement efforts, such as by simply mandating a minimal withdrawal time, have largely proven to be unsuccessful in significantly improving the polyp detection rate.

Innovations and breakthroughs

In this article, the authors showed that half of the screening colonoscopies in minority-predominant community were performed with inadequate bowel preparation quality. Moreover, the rate remained unchanged over the years, even though some providers started new methods of preparation. The authors then showed that prolonged colonoscope withdrawal by endoscopists practicing in this community was beneficial for the majority of cases, except for those with very poor and excellent bowel preparation qualities.

Applications

The findings of this study suggest aborting screening colonoscopy procedure in those with very poor bowel preparation quality because a prolonged duration of the colonoscope procedure is unlikely beneficial. On the other hand, prolonging colonoscope withdrawal time by more than the recommended duration in patients with an excellent quality of bowel preparation increases sedation time without benefits in polyp detection.

Terminology

A colonoscopy is an endoscopic procedure to detect and remove polyps in the large bowel (colon). Polyps in the colon have potential to become cancer. Detail evaluation of the colon is performed while withdrawing the colonoscope after reaching the beginning segment of the colon. Bowel preparation quality is considered unsatisfactory or very poor if the colon contains solid stool that does not clear with washing and suctioning. In this situation, more than 15% of the large bowel wall is not seen. If the detail of the colonic wall is clearly visible without washing, then the bowel preparation quality is considered to be excellent.

Peer review

It provides new information, particularly for young gastroenterologists and other doctors regarding polyp screening policies. It is a very interesting article and is well documented.

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CLINICAL TRIALS STUDY

Using motion capture to assess colonoscopy experience level

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Abstract

AIM: To study technical skills of colonoscopists using a Microsoft Kinect™ for motion analysis to develop a tool to guide colonoscopy education.

RESULTS: Ten experienced endoscopists (gastroenterologists, *n* = 2; colorectal surgeons, *n* = 8) and 11 novices participated in the study. A Microsoft Kinect ™ recorded the movements of the participants during the insertion of the colonoscope. We used a modified script from Microsoft to record skeletal data. Data were saved and later transferred to MatLab for analysis and the calculation of statistics. The test was performed on a physical model, specifically the "Kagaku Colonoscope Training Model" (Kyoto Kagaku Co. Ltd, Kyoto, Japan). After the introduction to the scope and colonoscopy model, the test was performed. Seven metrics were analyzed to find discriminative motion patterns between the novice and experienced endoscopists: hand distance from gurney, number of times the right hand was used to control the small wheel of the colonoscope, angulation of elbows, position of hands in relation to body posture, angulation of body posture in relation to the anus, mean distance between the hands and percentage of time the hands were approximated to each other.

RESULTS: Four of the seven metrics showed discriminatory ability: mean distance between hands [45 cm for experienced endoscopists (SD 2) *vs* 37 cm for novice endoscopists (SD 6)], percentage of time in which the two hands were within 25 cm of each other [5% for experienced endoscopists (SD 4) *vs* 12% for novice endoscopists (SD 9)], the level of the right hand below the sighting line (z-axis) (25 cm for experienced endoscopists *vs* 36 cm for novice endoscopists, $P < 0.05$) and the level of the left hand below the z-axis (6 cm for experienced endoscopists *vs* 15 cm for novice endoscopists, $P < 0.05$). By plotting the distributions of the percentages for each group, we determined the best discriminatory value between the groups. A pass score was set at the intersection of the distributions, and the consequences of the standard were explored for each test. By using the contrasting group method, we showed a discriminatory value of Z = 1.51 to be the pass/fail value of the data showing discriminatory ability. The pass score allowed all ten experienced endoscopists as well as five novice endoscopists to pass the test.

CONCLUSION: Identified metrics can be used to discriminate between experienced and novice endoscopists and to provide non-biased feedback. Whether it is possible to use this tool to train novices in a clinical setting requires further study.

Key words: Colonoscopy; Assessment; Simulation; Motion-capture; Motion-analysis

Core tip: Motion capture for motion analysis can be

used to discriminate between experienced and novice performers of colonoscopy. We analyzed the motion patterns of the technical procedure of inserting the colonoscope from anus to cecum in a simulation set-up. The technical differences between novice and experienced endoscopists observed in this study are important because they can help shape skills that will lead to competence in colonoscopy. In the future, this technique might be useful in the training and education of future colonoscopists in a clinical setting.

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INTRODUCTION

Screening programs for colorectal cancer and concern for patient safety have increased the importance of training endoscopists for competency in colonoscopy. The workload of existing endoscopy units is often high, with units performing an increasing number of endoscopies in addition to supervising, training and instructing future endoscopists. The quality of colonoscopies was questioned in an investigation of 68 endoscopy units in the United Kingdom with a cecal intubation rate of 56%. Only 17% of the endoscopists had supervised training during their introduction to colonoscopy, and only 33% attended a colonoscopy course[1]. In Denmark, colonoscopy competence is solely based upon educational level, such as having a specialized degree in gastroenterology and/or surgery. The number of colonoscopies performed has conventionally defined technical competence in colonoscopy, and a threshold number of up to 275-500 has been suggested[2,3]. Previous methods for assessing skills in colonoscopy have been based upon subjective expert ratings, and previous tools have been based upon the procedural endpoints, time to cecum, depth of insertion or complication rate of therapeutic procedures[4-6]. No automatic assessment tools have been developed, although it has been noted that an optimal assessment tool in surgical skills should be based upon objective and structured criteria[7]. However, some progress has been made with regards to a benchmarked curriculum for virtual reality colonoscopy simulators[8].

Colonoscopy is very much dependent upon manual dexterity, correct stance and hand-eye coordination. The correct way to perform a colonoscopy is greatly debated, and some variations have been noted among experts advocating for the single-handed technique[9-13]. Video imaging has been found to be valuable in assessing competence in surgical skills[7], and video-based judgment of the handling of endoscopes is one of the main basic colonoscopy procedures tested with the "Direct Observation of Procedural Skills Score (DOPS)"[14].

It is a well-known but unproven fact among professional gastroenterologists that the stance of the performer shows the level of competence. Defining a "correct" basic handling in colonoscopy is not easy, but certain facts are clear: when adhering to the single-handed technique[9,10,13], the procedure should be conducted in a relaxed fashion with a straight scope, with minimal discomfort for the endoscopist as well as for the patient. Concerning movements of the tip of the scope, torque steering and steering with the small wheel of the colonoscope has very little effect when the tip is angulated[15].

The correct single-handed technique has been tested by video imaging with an objective structured video assessment tool where instrument grip, tip steering, and letting go of the instrumental shaft all were found to correlate with the competence level of the endoscopist[9]. The same basic colonoscopy metrics were found to improve significantly in an intensive training program[10].

Motion analysis has been used to teach correct skiing technique in downhill skiing to prevent injuries[16] and to correct golf swings[17]. Motion analysis can also be used to determine joint movements in different procedures, such as walking in high-heeled shoes to explain the occurrence of gait related diseases[18]. We speculate that motion analysis could also be used to teach correct movements in colonoscopy performance, if correct movements can be identified and verified.

In medicine, motion analysis has been used to identify skilled performers in emergent endotracheal intubation in physical models[19] as well as in an infant airway trainer[20]. Previously, motion analysis demanded the use of sensors on the body, making analysis of movements a costly process. In 2012, Microsoft launched the Microsoft Kinect (MS Kinect) system for Windows, designed for the XBOX gaming platform. The MS Kinect camera has become increasingly popular in many areas aside from entertainment. It provides a quick, cheap and easy way of analyzing position and mapping 3-dimensional (3D) pose data, providing skeletal movement tracking. The accuracy of the system as a peripheral device measuring 3D depth is estimated to be 1-4 cm at a range of 1-4 m[21].

The aim of this study was to use the MS Kinect system to automatically record and analyze the components of the basic techniques of endoscopists (experienced endoscopists and novices), selecting discriminatory metrics to develop a tool which can monitor competence in endoscopists and guide education in a non-biased way.

MATERIALS AND METHODS

Participants

Ten consultants experienced in endoscopy (gastroenterologists, n = 2; colorectal surgeons, n = 8) and eleven novices participated in the study. Novices were recruited from fellows in gastroenterology and gastroenterological surgery during their first or second year of fellowship and had very limited experience in colonoscopy (median 0 procedures, range 0-2). The experienced group had an average of 18.3 years of endoscopic experience

Table 1 Demographic details on the participation physicians

	Sex		Age, yr		Colonoscopy experience		Colonoscopies performed in past 12 mo	
	Male	Female	Median	Range	Median	Range	Median	Range
Novices (n = 11)	4	7	32	(28-37)	0	(0-2)	0	(0-2)
Experienced endoscopists (n = 10)	8	2	55	(42-63)	2000	(350-4000)	52.5	(0-450)

(range 7-30) and had performed a median of 2000 (range 350-4000) colonoscopies, including a median of 75 (range 0-450) colonoscopies within the last year (Table 1). All participants were recruited and tested between November 2012 and March 2013.

Study set-up

We used a virtual reality simulator for the introduction to the functions of the colonoscope (GI Mentor, Simbionix Corporation, United States). For the test, we used the Kagaku Colonoscope Training Model (Kyoto Kagaku Co. Ltd, Kyoto, Japan) and a colonoscope (Olympus™ CF 180AL) with air insufflation, suction-water knobs and a scope guide from Olympus. The physical model consisted of a flexible rubber "colon" tube inside of a life-size mannequin. The colon tube could be adjusted into 6 different positions using Velcro-strips and rubber bands. Tasks 1 (test introduction) and 3 (test) were chosen for this study. Task 1 was a technically easy procedure, whereas task 3 was more challenging, with a loop formation in the sigmoid colon. The test setting was a fixed set up in a dedicated room and was not changed during the study period.

Data collection

Testing was conducted in a medical simulation center. The novices were introduced to the functions of the colonoscope including handling the colonoscope, using the controls (*i.e.*, dials, insufflation, suction, and water), manipulating the endoscope tip, and torque steering in a virtual-reality simulator. The training session was 1 hour. All participants were asked to fill out a brief questionnaire, which included demographics, such as gender, age, years of endoscopic experience and the number of colonoscopies performed during the past 12 mo. A letter of acceptance of participation was handed out, signed and returned prior to the test. Participants were instructed to treat the model as if it were a real patient. The participants were informed that their movements would be recorded but were given no details of which metrics would be measured. They were given a maximum of 15 min to perform the procedure. A Kinect camera recorded the movements of the participant during insertion of the scope. Recording was initiated at intubation of the rectum and stopped when the scope reached the cecum.

Microsoft Kinect

The Kinect camera consists of a series of external sensors for image capturing and is motorized to make the box adjustable. The sensors are able to detect movements without requiring the participants to wear tracking sensors.

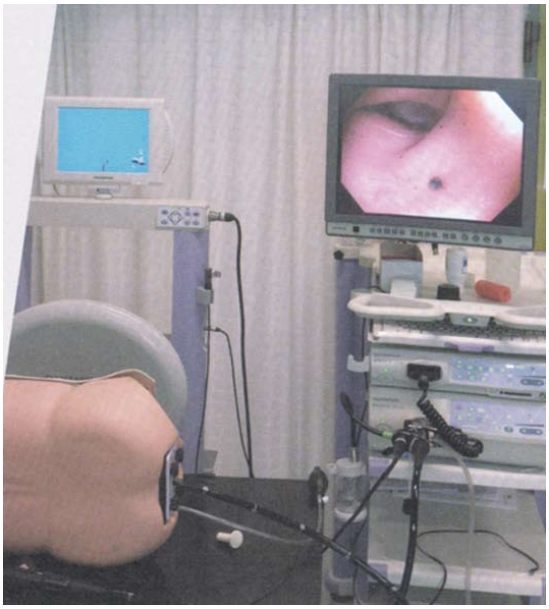

Figure 1 The simulator set-up. The Kinect was placed behind the two screens.

The Kinect creates a map of reflections from the person in the scene, which can be used for skeleton analysis. We used a modified script from Microsoft for recording skeletal XYZ-data. Data were saved and later transferred to MatLab® 2012a for analysis and the calculation of statistics. The range of the Kinect system for depth analysis is 1.2-3.5 m; the test set-up was adjusted to this distance. The box was placed above the endoscopy screen pointing at the chest of the participants, producing an image of the upper part of the body (Figure 1). The setup was not adjusted according to the height of the participants but all participants were within the range of the camera. The coordinates of the Kinect system are shown in Figure 2. The Z-axis was pointed at the chest, and the X-axis was longitudinal to the gurney.

Measured metrics

Validated tools, such as DOPS, suggest metrics related to basic techniques, such as the correct use of the left and right hands and understanding looping and cecal intubation[10]. However, there is no defined correct way of handling the scope during insertion. We chose a number of measures, skeletal angles and joint movements we thought appropriate to the procedures based on the literature[15].

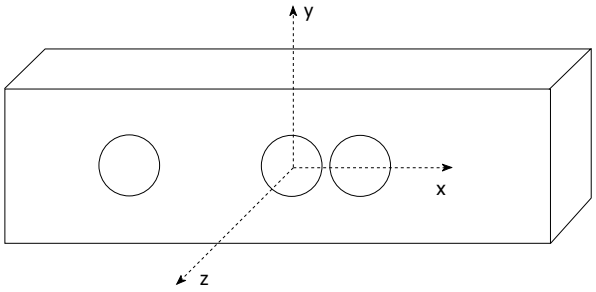

Figure 2 3D coordinates of the Kinect system.

Metrics used for motion analysis were the distance of the right and left hands from the gurney, the number of times the right hand was used to control the small wheel (distance between hands less than 25 cm), the angulation of the right and left elbows, the position of the hands in relation to the torso, the angulation of body posture in relation to the orifice, the mean distance of the hands from each other during the procedure and the percentage of time the hands were approximated. Measurements were conducted at 30 frames per second, and for each person, a mean of values was calculated in relation to coordinates of the MS Kinect.

Statistical analysis

All variables showing statistically significant differences between novices and experienced operators were identified using independent sample *t*-tests. The means and standard deviations of the experienced group were used to transform variables with discriminative ability into Z-scores. These Z-scores, when discriminatory, were intended to be averaged into a single score for each participant; *i.e.*, a score of 2 indicated that the participant, on average, was two standard deviations off the "gold standard", defined by the mean of experienced operators. A pass-fail standard was set using the contrasting groups method to further explore the ability of this aggregated score to discriminate between the two groups.

An independent samples *t*-test, Mann-Whitney test and Levene's test for equality of variance were performed to compare the performances of the two groups. Spearman's rho was used for non-parametric correlation analysis.

Statistical analysis was performed using a statistical software package (r-project.org, R v 3.0.2; MatLab® 2012a). Differences were considered to be statistically significant for P values < 0.05.

RESULTS

The two groups differed in gender (experienced endoscopists: 2 females, 8 males; novices: 7 females, and 4 males) (NS, Fisher's test) and age. For details see Table 1.

Only four of our seven metrics showed discriminatory ability between novice endoscopists and experienced endoscopists in the *t*-test (test of mean), and only two showed a difference in group-variance.

Table 2 Metrics analysed for discriminatory ability

Kinect metrics	Experienced endoscopist	Novice	Levene's test	*P* value
Percentage of time with hands closer than 25 cm (%)	7	23	0.048	0.02
Distance between hands (cm)	45	37	0.09	0.01
Angle of shoulders (degrees)	17	20	0.95	0.38
Right hand below z-line (cm)	25	36	0.95	0.01
Mean distance shoulder-hand (cm)	31	31		
Left hand above z-line (cm)	6	15	0.03	0.005
Mean distance: shoulder-hand (cm)	32	31		
Left elbow (degrees)	91	92	0.86	0.81
Right elbow (degrees)	144	140	0.55	0.55
Height participants (cm)	39	30	0.08	0.02
Compared to coordinates				

Three metrics: "angulation of right elbow," "angulation of left elbow" and "angulation of shoulders to the anus of physical model" did not show discriminatory ability.

We found discriminatory values for the following metrics: "level of left hand" and "level of right hand" below the z-axis (experienced: 6 cm for the left hand; novices: 15 cm for the left hand, $P < 0.05$; experienced: 25 cm for the right hand; novices: 36 cm for the right hand, $P < 0.05$). The difference subsided when correcting for the height of the person by analyzing the distance of the left and right hands from the left and right shoulders accordingly (31 cm *vs* 32 cm, NS). The two groups differed in height when shoulder height was analyzed. For details see Table 2.

Two metrics showed discriminatory ability: "mean distance between hands" [experienced: 45 cm (SD 2); novices: 37 cm (SD 6)] and "percentage of time with hands less than 25 cm apart" [experienced: 5% (SD 4); novices: 12% (SD 9)].

Absolute Z-scores (average standard deviations from the "gold standard") were calculated for each of the discriminatory metrics and summed to a total mean Z-score for each participant. For details, see Table 3.

By plotting the distributions for each group, we could determine the best discriminatory value between the groups. The pass score was set at the intersection of the distributions, and the consequence of the standard was explored for each test. By using this contrasting group method, we showed a discriminatory value of Z = 1.51 to be the pass score. The pass score allowed all of the experienced as well as the five novices to pass the test (Figure 3).

Nine of ten of the experienced operators reached the cecum within 15 min (the cut-off time), as did seven out of 11 novices (64%). Comparing Z-scores, pass *vs* cecal intubation ability's positive PV for a passing Z-score was found to be 80%, while the negative PV for cecal intubation for a failed Z-score was 33%.

Table 3 Experience correlated to pass score and cecal intubation rate

Test person	Competence	Total colonoscopies	Colonoscopies in last year	Z mean	Z-score passed	Cecal intubation
1	Experienced Endoscopist	3000	300	1.15	Yes	Yes
2	Experienced endoscopist	400	10	1.32	Yes	Yes
3	Experienced endoscopist	2000	0	1.25	Yes	Yes
4	Experienced endoscopist	1000	17	0.08	Yes	Yes
5	Experienced endoscopist	1700	150	0.30	Yes	Yes
6	Experienced endoscopist	4000	232	0.70	Yes	Yes
7	Experienced endoscopist	3000	14	0.78	Yes	Yes
8	Experienced endoscopist	2000	450	0.76	Yes	Yes
9	Experienced endoscopist	2000	75	0.82	Yes	Yes
10	Experienced endoscopist	350	30	0.73	Yes	Yes
11	Novice	0	0	1.54	No	No
12	Novice	0	0	1.48	Yes	No
13	Novice	0	0	1.28	Yes	Yes
14	Novice	0	0	2.26	No	Yes
15	Novice	1	1	6.19	No	Yes
16	Novice	0	0	0.27	Yes	Yes
17	Novice	0	0	6.50	No	No
18	Novice	0	0	5.25	No	Yes
19	Novice	0	0	1.17	Yes	No
20	Novice	0	0	3.25	No	Yes
21	Novice	2	2	0.65	Yes	No

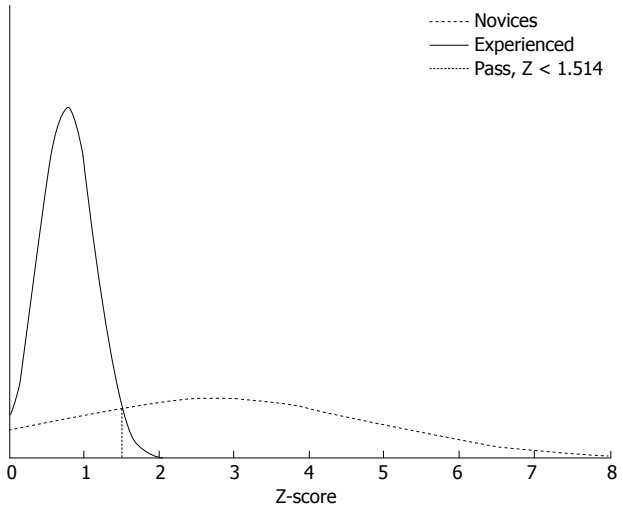

Figure 3 Establishing a pass/fail standard using the contrasting-groups method. The distribution of scores of novices (dotted line) and experienced (solid line). The pass score (Z-1,51) is set at the intersection of the score distributions of the two groups.

There was no difference in the novices who reached the cecum and the novices who did not reach the cecum in regards to percentage of time when the hands were less than 25 cm apart (14%). When measuring the distance between hands, there were no group differences among the novices (37 cm).

Time to reach the cecum was measured. A positive correlation Rho was found for "percentage of time with hands too close," "hand distance" and "cecal intubation time" (Rho = -0.58; $P = 0.005$ and Rho = 0.60; $P = 0.004$).

There was no correlation between the aggregated Z-score and time to cecum (Rho = 0.40; NS). However, when analyzing the correlation between the numbers of colonoscopies performed in the past year (Log routine) and the aggregated Z-score, a correlation was found (Rho = -0.54; $P = 0.01$).

DISCUSSION

Our data showed a difference in motion patterns of the colonoscopy procedure when comparing novices to experienced endoscopists. By using the MS Kinect, we could identify a common stance used by experienced endoscopists. Our data made it possible to note how the novices handled the colonoscope as they tried to control the tip. We found that excessive correction movements halted the progress of the colonoscope.

We found no correlation between the total score and time to cecum, which indicates that progression does not entirely depend on manual handling of the control dials of the colonoscope. We did, however, find a correlation between current routine (past years experience) and the Z-score, suggesting that other aspects of the steering process must be important. The reason for this might be the ability to keep the scope straight. Having a straight scope inside of the patient depends on a scope without loops and bends outside of the patient and a slack loop between hands. We found that the distance between hands was significantly wider in the experienced group, which might make "torque steering" easier[15]. The MS Kinect could not record the motion pattern of torque steering.

Assessment tools based on tri-split video monitoring and evaluation by trained judges have been made and validated by others[9,22]. DOPS assesses different domains of the colonoscopy procedure: basic handling of the colonoscope, such as "grip of instrument with accurate finger/thumb," "control of wheels," "tip steering" and "manipulation of the shaft".

The metric "distance between hands" was a surrogate measure of keeping the scope straight. We considered our data for "percentage of time with hands too close"

to be a surrogate measure of using both hands on the control dials (distance less than 25 cm). The DOPS metric "incorrect use of hand grip" was found to be one of the most significant metrics, showing improvement with a week of intensive training[10]. Using both hands on the steering wheel stopped the progression of the scope. We demonstrated an unbiased measure using "percentage of time with hands too close" to assess this parameter.

The ability to reach the control dials with the thumb can be challenging because the grip of the standard colonoscope has been developed for large hands. Endoscopists compensate by bringing the right hand up to help adjust the control dials. Cohen and colleges made an informative survey and found that 23% of fellow gastroenterologists felt that they had some difficulties in reaching and manipulating the horizontal control dial (small wheel). A considerable portion of the female fellows reported that their hands were too small to reach the horizontal control dial (40%), and nearly 80% reported that their hand size affected their ability to learn endoscopy[23]. The "left-hand grip"[12] and the "pinkie maneuver"[11] are methods to maneuver the control dials to compensate for this challenge. However, both methods result in a bended scope, which might negatively affect progression. Traditionally, ergonomic concerns have not played a large role in teaching the colonoscopy procedure. Tenosynovitis of the left thumb associated with overuse during endoscopy has been described (DeQuervain's syndrome), and this problem has increased with an increased number of procedures performed per endoscopist[24]. A solution to both problems could be the introduction of the scope-dock system developed for the ERCP procedure in colonoscopy. A docking system would allow for free handling of control dials simultaneous to torque steering and advancing the tip of the scope.

The aggregated score of our two significant metrics has demonstrated the ability to differentiate between experienced and novice endoscopists, and the pass score had a predictive value of 80% for reaching the cecum. Current routine in colonoscopy was highly correlated to the metrics with discriminatory ability. The combined Z-score, with a correlation coefficient of 0.54, made the Z-score an objective assessment tool to predict the ability to reach the cecum in a routine colonoscopy.

The advantage of the MS Kinect system is that it provides information on the motion pattern with an inexpensive and simple method[25]. The method has been found to be accurate in skeletal tracking of upper body movements as well as for joint measurements with an accuracy of 1-2 cm for a distance of up to 4 m[21].

Our assessment tool provides information that emphasizes that training should focus on handling the control dials, especially the small horizontal control dial, with the left hand and keeping a straight scope with a distance between the hands. Our data show that it was possible to recognize the motion pattern of experienced endoscopists by external motion capture and to distinguish the experienced from the novices in an objective way. We found a correlation between the current routine and the metrics with discriminatory ability, suggesting that correcting the stance might be relevant, not only in novices.

Whether it is possible to use this information from stance recognition and pose enforcement to train novices in a clinical setting remains to be determined, but this unbiased tool does provide useful information to guide teaching. Our tool might help colonoscopy trainees gain competence in the technical part of the colonoscopy procedure, which is the difficult and strenuous part of the procedure for the endoscopists, as well as for the patient.

COMMENTS

Background

Colonoscopy is a technically challenging procedure that requires the development of advanced psychomotor skills. During the past decade there has been increased focus on structured medical education and the assessment of procedural skills. Competence in colonoscopy has conventionally been defined as the number of colonoscopies performed or as rates of successful intubation of the cecum. Only a few attempts have been made to measure technical competence in colonoscopy. This study brings new objective information for learning technical skills of colonoscopy using motion capture.

Research frontiers

Motion analysis has been used in sports for decades. Using motion capture in colonoscopy provides new, useful, objective information to guide novices and those teaching colonoscopy so that competence in this procedure can be measured.

Innovations and breakthroughs

Previously, motion analysis required the use of sensors on the body, making the analysis of movements a costly process. In 2012, Microsoft launched the Microsoft Kinect (MS Kinect) system for Windows, designed for a gaming platform. The MS Kinect camera has become increasingly popular in many areas aside from entertainment and has been used in other areas of medical education.

Applications

Motion capture seems useful for obtaining objective measures to guide colonoscopy education and can be used in a clinical setting to provide unbiased feedback to guide novices and those teaching colonoscopy so that competence in this procedure measured by other gauges can be achieved.

Terminology

Motion capture: The process of recording the movement of people; Assessment tool: A method to assess performance; DOPS: Direct Observation of Procedural Skills Score is a validated assessment tool for the colonoscopy procedure.

Peer review

The authors address an important and relevant topic in today's teaching and learning of endoscopy and bring new objective information for learning its technical skills. The paper is very interesting.

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META-ANALYSIS

Early precut sphincterotomy and the risk of endoscopic retrograde cholangiopancreatography related complications: An updated meta-analysis

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Abstract

AIM: To study the cannulation and complication rates of early pre-cut sphincterotomy *vs* persistent attempts at cannulation by standard approach.

METHODS: Systematic search of PubMed, EMBASE, Web of Science, and the Cochrane Library for relevant studies published up to February 2013. The main outcome measurements were cannulation rates and post-endoscopic retrograde cholangiopancreatography (ERCP) complications. A comprehensive systematic search of the Cochrane library, PubMed, Google scholar, Scopus, National Institutes of Health, meta-register of controlled trials and published proceedings from major Gastroenterology journals and meetings until February 2013 was conducted using keywords. All Prospective randomized controlled trials (RCT) studies which met our inclusion criteria were included in the analysis. Prospective non-randomized studies and retrospective studies were excluded from our meta-analysis. The main outcomes of interest were post-ERCP pancreatitis, overall complication rates including cholangitis, ERCP-related bleeding, perforation and cannulation success rates.

RESULTS: Seven RCTs with a total of 1039 patients were included in the meta-analysis based on selection criteria. The overall cannulation rate was 90% in the pre-cut sphincterotomy *vs* 86.3% in the persistent attempts group (OR = 1.98; 95%CI: 0.70-5.65). The risk of post-ERCP pancreatitis (PEP) was not different between the two groups (3.9% in the pre-cut sphincterotomy *vs* 6.1% in the persistent attempts group, OR = 0.58, 95%CI: 0.32-1.05). Similarly, there was no statistically significant difference between the groups for overall complication rate including PEP, cholangitis, bleeding, and perforation (6.2% *vs* 6.9%, OR = 0.85, 95%CI: 0.51-1.41).

CONCLUSION: This meta-analysis suggests that pre-cut sphincterotomy and persistent attempts at cannulation are comparable in terms of overall complication rates. Early pre-cut implementation does not increase PEP complications.

Key words: Post-cholangiopancreatography pancreatitis; Pre-cut sphincterotomy; Persistent attempts; Meta analysis

Core tip: Selective cannulation of the bile duct remains the limiting step in therapeutic post-endoscopic retrograde cholangiopancreatography (ERCP). Greater than 90% of cannulation is achieved through standard techniques. In 10% of patients, cannulation is difficult and requires additional techniques such as pre-cut

sphincterotomy. Early use of pre-cut sphincterotomy is suggested as a means to prevent excessive and repetitive papillary trauma which may in turn increase the risk of post-ERCP pancreatitis. The use of pre-cut sphincterotomy has been considered to increase risk of post-ERCP complications, in particular post-ERCP pancreatitis. We studied the literature on the use of pre-cut sphincterotomy in biliary access. Our meta-analysis showed that pre-cut sphincterotomy and persistent attempts at cannulation are comparable in terms of overall complication rates including post-ERCP pancreatitis. Early pre-cut implementation does not increase PEP complications.

Navaneethan U, Konjeti R, Venkatesh PGK, Sanaka MR, Parsi MA. Early precut sphincterotomy and the risk of endoscopic retrograde cholangiopancreatography related complications: An updated meta-analysis. *World J Gastrointest Endosc* 2014; 6(5): 200-208 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i5/200.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i5.200

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) has been widely used for treatment of a variety of biliary disorders and cannulation of the bile duct remains one of the most important steps for successful therapeutic endoscopy. The success of biliary cannulation depends on several factors including patient anatomy, utilization of specialized catheters, and the skill and experience of the endoscopist[1]. Deep biliary cannulation by an experienced endoscopist using standard cannulation techniques is successful in approximately 90% of the cases[1]. Biliary cannulation becomes difficult in about 5%-10% of the cases[2,3] especially in patients with abnormal anatomy, ampullary or pancreatic tumors, and periampullary diverticuli. Precut sphincterotomy, also referred to as needle knife sphincterotomy (NKS), has been advocated in situations where routine biliary cannulation has been unsuccessful. The presumed risks and morbidity associated with NKS, particularly risk of post-ERCP pancreatitis (PEP) has discouraged use of this technique in patients with difficult biliary access[4]. The assessment of this risk, however, is confounded by pre-cut sphincterotomy being done as a last resort after repeated failed attempts at biliary cannulation and in some cases repeated inadvertent pancreatic duct (PD) cannulations. Repeated failed attempts at biliary cannulation and repeated pancreatic duct cannulations have been shown to be independently associated with a higher incidence of PEP[5-7]. In addition to PEP, reported complications of NKS are bleeding[8] and perforation[9]. The main goal of therapeutic ERCP is to achieve biliary cannulation with least possible adverse events. Early use of pre-cut sphincterotomy is suggested as a means to prevent excessive and repetitive papillary trauma which may in turn increase the risk of PEP. The few randomized controlled trials (RCTs) that have tried to assess the differences in the complication rates between early pre-cut sphincterotomy and persistent cannulation groups, have shown variable results and are limited by small number of patients and therefore inadequate power to demonstrate any potential differences between the groups[10-12].

An earlier meta-analysis demonstrated that early pre-cut sphincterotomy reduces PEP risk but not the overall complication rate or cannulation success[13]. Subsequent to this publication, another RCT has been published[14]. This study showed that early use of NKS during difficult cannulation does not increase the risk of PEP. Given the importance of this topic for the clinical practice of ERCP, we sought to perform an updated meta-analysis to study the differences in cannulation rates, PEP and overall complication risk between early pre-cut sphincterotomy and persistent attempts at cannulation, taking the new randomized study into consideration.

MATERIALS AND METHODS

Search strategy

Two authors (Navaneethan U, Konjeti R) independently conducted a comprehensive search of the Cochrane library, PUBMED, Google scholar, Scopus, National Institutes of Health, meta-register of controlled trials and published proceedings from major Gastroenterology journals and meetings until February 2013. The search was conducted using the key words endoscopic retrograde cholangiopancreatography, ERCP, precut, cannulation, needle-knife, papillotomy, sphincterotomy, fistulotomy. All relevant articles irrespective of language, year of publication, type of publication, or publication status were included. The titles and abstracts of all potentially relevant studies were screened for eligibility. The reference lists of studies of interest were then manually reviewed for additional articles. In the case of studies with incomplete information, the principal authors were contacted to obtain additional data.

We applied the following inclusion criteria for identifying studies for our analysis: (1) prospective RCTs comparing cannulation techniques: "early precut" group in which precutting was done early during the procedure and the "persistent attempts" group in which persistent attempts were made with standard cannulation; and (2) Comparison of major complications (PEP, cholangitis, ERCP-related bleeding and perforation) between the two groups. Our outcomes of interest were PEP, overall complication rates and cannulation rates. Prospective non-randomized studies and retrospective studies were excluded from our meta-analysis.

Quality assessment

The quality of the studies was assessed according to quality criteria (Table 1). Simple and direct questions were organized to investigate each quality measure by two independent investigators (Navaneethan U, Konjeti R).

Statistical analysis

Data was extracted by two independent reviewers with

Table 1 Study quality characteristics of randomized controlled trials

Ref.	Were patients randomized	Was generation of allocation sequence adequate	Eligibility criteria mentioned	Both patients and clinicians blinded	Participants baseline characteristics similar in both groups	Treatment allocation concealed	Study adequately powered to asses significant clinical outcome
Tang *et al*[10]	Yes	Yes	Yes	Partially fulfilled	Yes	Yes	No
Zhou *et al*[19]	Yes	Yes	Partially	Partially fulfilled	Yes	Yes	N/A
de Weerth *et al*[12]	Yes	N/A	Yes	Partially fulfilled	Yes	N/A	N/A
Khatibian *et al*[18]	Yes	Yes	Yes	Partially fulfilled	Yes	Yes	Partially
Manes *et al*[20]	Yes	Yes	Yes	Partially fulfilled	Yes	N/A	No
Cennamo *et al*[11]	Yes	Yes	Yes	Partially fulfilled	Yes	Yes	No
Swan *et al*[14]	Yes	Yes	Yes	Yes	Yes	Yes	No

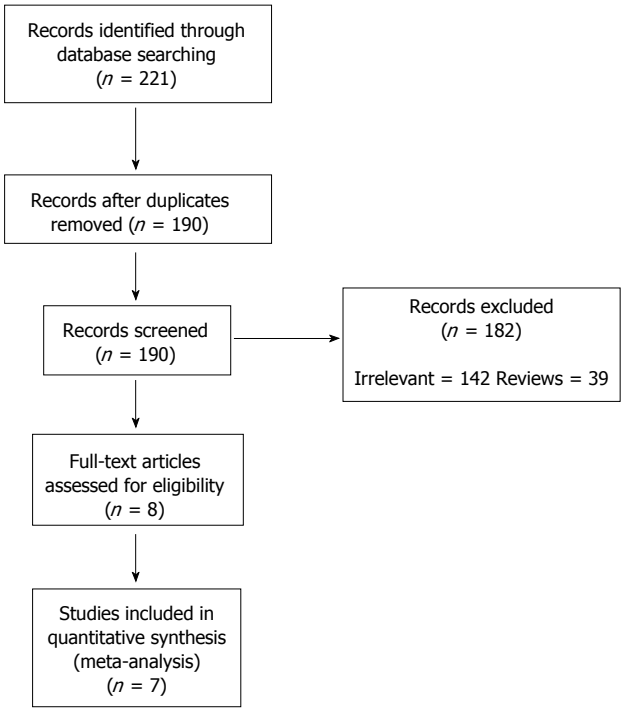


Figure 1 Flow chart demonstrating the literature search for the meta-analysis.

discrepancies settled by a third investigator (Sanaka MR). We performed the review and meta-analyses following the recommendations of The Cochrane Collaboration[15]. The analyses were performed using RevMan version 5.1. Binary outcomes were expressed as relative risks (RR) and continuous outcomes as median or mean difference, with 95%CI. Data was analyzed by fixed or random-effects model depending on heterogeneity[16]. Regression analyses were performed to estimate funnel plot asymmetry[17]. In our analysis, heterogeneity was explored by the chi-square test, with significance set at a P value of 0.05, and measured by I^2[15]. A sensitivity analysis using random effects models for the overall deep-biliary cannulation rate was also performed.

RESULTS

Literature search and characteristics of included studies

Two-hundred and twenty one potentially relevant studies were identified by our primary search of the electronic databases for published work on the subject. Of these studies, 214 were excluded after further review of the title and abstract for irrelevant topics, duplication of the reports, prospective non-RCTs or not meeting inclusion criteria. After careful review, 7 RCTs were eligible for meta-analysis. The detailed process of this literature search is shown in Figure 1. The characteristic of each included study is shown in Table 2.

The study quality characteristics are discussed in Table 1. The recent RCT by Swan *et al*[14] was a blinded study. Immediate precut was performed in two studies in patients randomized to precut arm without any previous cannulation attempts[12,18]. In the remaining 5 RCTs, pre-cut randomized patients had 5-12 min of biliary cannulation attempts[10,11,14,19,20], or if there was three accidental pancreatic duct cannulations[11,19]. In the study by Swan *et al*[14], endoscopists placed a pancreatic stent (Zimmon; Cook Medical, Bloomington, IN; single pigtail, 2-5 cm 5F) before pre-cut sphincterotomy if the PD had been cannulated at least twice. If the PD had not been cannulated during the biliary cannulation attempt(s), a PD stent was not placed. There was no significant difference in the use of PD stents between the 2 randomized groups; 15 of 34 (44%) in the persistent attempts group and 23 of 39 (59%) in the pre-cut sphincterotomy arm. Similarly, there was no statistical difference in the use of PD stents in the successful continued cannulation group *vs* those in the continued cannulation group who required crossover to pre-cut sphincterotomy; 5 of 12 (41%) *vs* 10 of 22 (45%) respectively. In rest of the studies pancreatic stent placement was not implemented in both the randomized arms. Six studies[10-12,14,18,20] defined procedure-related complications.

The techniques employed for cannulation and precut were different in the included studies (Table 3). In the persistent attempts group, the wire-guided technique was implemented to achieve deep biliary cannulation in most of the studies[11,12,14,18].

Comparative pancreatitis and overall complication rates between early precut and persistent attempt groups

Seven RCTs compared the overall complication rates (Table 1). The baseline characteristics of the studies are presented in detail in Tables 1 and 2. In our meta-analysis (Figure 2A) including 7 studies, the overall complication rates including PEP, bleeding and perforation were

Table 2 Study characteristics of randomized controlled trials

Ref.	Country	Center involved	No. of patients screened	Patients allocated to early precut/persistent attempts
Tang *et al*[10]	Canada	Single center	642	32/30
Zhou *et al*[19]	China	Single center	948	43/48
de Weerth *et al*[12]	Germany	Single center	291	145/146
Khatibian et al[18]	Iran	Single center	242	106/112
Manes *et al*[20]	Italy	Multicenter	1654	80/78
Cennamo *et al*[11]	Italy	Single center	1078	36/110
Swan *et al*[14]	Australia	Single center	464	39/34

Table 3 Techniques of pre-cut in randomized controlled trials

Ref.	Technique used in persistent attempts group	Timing of early precut	Precut technique	Timing of persistent attempts
Tang *et al*[10]	Non-wire guided sphincterotome	Biliary cannulation failed within 12 min	Needle knife precut starting at orifice	Biliary cannulation failed within 15 min
Zhou *et al*[19]	Non-wire guided and wire guided sphincterotome	Biliary cannulation failed within 10 min or 3 unintended pancreatic duct cannulation	Needle knife precut starting at orifice and fistulotomy	Not available
de Weerth *et al*[12]	Wire guided sphincterotome	Immediate precut for direct bile duct access	Erlangen type sphincterotome on the papillary roof	Biliary cannulation failed within 10 min or 3 unintended pancreatic duct cannulation
Khatibian *et al*[18]	Wire guided sphincterotome	Immediate needle knife fistulotomy for direct CBD access	Needle knife fistulotomy	Biliary cannulation failed within 15 min
Manes *et al*[20]	Non-wire guided and wire guided sphincterotome	Biliary cannulation failed within 10 min	Needle knife fistulotomy	Biliary cannulation failed within 10 min
Cennamo *et al*[11]	Wire guided sphincterotome	Biliary cannulation failed within 5 min or 3 unintended pancreatic duct cannulation	Needle knife precut starting at orifice	Biliary cannulation failed within 20 min post randomization
Swan *et al*[14]	Wire guided sphincterotome	Biliary cannulation failed within 10 min	Needle knife precut starting from superior aspect of orifice	Biliary cannulation failed within 10 min post randomization

6.2% (30 cases out of 481 patients) in precut group and 6.9% (39 cases out of 558 patients) in persistent attempts group. The pooled analysis didn't show any statistically significant difference between the two groups with an OR 0.85 (95%CI: 0.51-1.41). As the pooled estimation didn't showed significant heterogeneity a fixed-effect model was used in this analysis. The risk of PEP was 3.9% (19 cases out of 481 patients) in precut group and 6.1 % (34 cases out of 558 patients) in the persistent attempts group (Figure 3A). Although a trend towards a lower incidence of PEP in the early precut groups was observed, the pooled analysis didn't show any statistically significant difference between the two groups with an OR 0.59 (95%CI: 0.32-1.07).

The bleeding rate was found to be 1.8% (9 cases out of 481) in precut group and 0.9 % (5 cases out of 558 patients) in the persistent attempts group. The perforation rate was found to be 0.4% (2 cases out of 481) in precut group and 0.18 % (1 case out of 558 patients) in persistent attempts group. An analysis for cholangitis as a complication was not done as rates were not reported in two studies. The numbers were very small to calculate the pooled OR for these complications separately.

Cannulation rates

The overall cannulation rate was found to be 90% in pre-cut sphincterotomy group and 86.3% in persistent attempts group. The pooled analysis didn't show any significant difference between the two groups with an OR 1.98 (95%CI: 0.70-5.65) (Figure 4A). Statistical tests did show the presence of between-study heterogeneity and as such a random effects model was used to account for this heterogeneity.

Publication bias

Visual inspection of funnel plots in Figure 5 (for overall complications and post-ERCP pancreatitis) further confirms that publication bias is not a major determinant in this meta-analysis.

Subgroup analysis

In two studies included in our meta-analysis, pre-cut was performed even without attempts at cannulation with the standard approach[12,18]. The other studies had varying periods of cannulation attempts before randomization, reflecting real clinical practice. After excluding the two studies in which direct pre-cut was performed, the results were unchanged (Figure 2B, 3B and 4B).

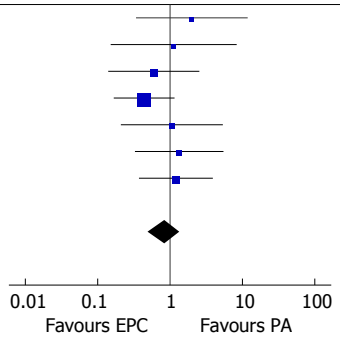
DISCUSSION

Despite advances in ERCP, failure of biliary cannulation and PEP remain two major issues where room for improvement exists. In experienced hands, successful

A

Study or subgroup	EPC Events	EPC Total	PA Events	PA Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Tang 2005	4	32	2	30	5.6%	2.00 [0.34, 11.82]	2005
Zhou 2006	2	43	2	48	5.5%	1.12 [0.15, 8.33]	2006
De Weerth 2006	3	145	5	146	15.0%	0.60 [0.14, 2.54]	2006
Khatibian 2008	3	106	3	112	8.7%	1.06 [0.21, 5.36]	2008
Manes 2008	7	80	14	78	39.8%	0.44 [0.17, 1.15]	2008
Cennamo 2009	3	36	7	110	9.7%	1.34 [0.33, 5.47]	2009
Swan 2013	8	39	6	34	15.7%	1.20 [0.37, 3.90]	2013
Total (95%CI)		481		558	100.0%	0.85 [0.51, 1.41]	
Total events	30		39				

Heterogeneity: χ^2 = 3.80, df = 6 (P = 0.70); I^2 = 0%
Test for overall effect: Z = 0.64 (P = 0.53)



B

Study or subgroup	EPC Events	EPC Total	PA Events	PA Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Tang 2005	4	32	2	30	7.3%	2.00 [0.34, 11.82]	2005
Zhou 2006	2	43	2	48	7.3%	1.12 [0.15, 8.33]	2006
Manes 2008	7	80	14	78	52.2%	0.44 [0.17, 1.15]	2008
Cennamo 2009	3	36	7	110	12.8%	1.34 [0.33, 5.47]	2009
Swan 2013	8	39	6	34	20.5%	1.20 [0.37, 3.90]	2013
Total (95%CI)		230		300	100.0%	0.87 [0.49, 1.56]	
Total events	24		31				

Heterogeneity: χ^2 = 3.49, df = 4 (P = 0.48); I^2 = 0%
Test for overall effect: Z = 0.46 (P = 0.65)

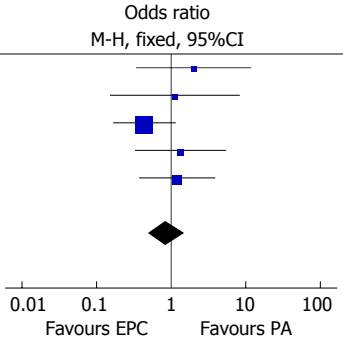
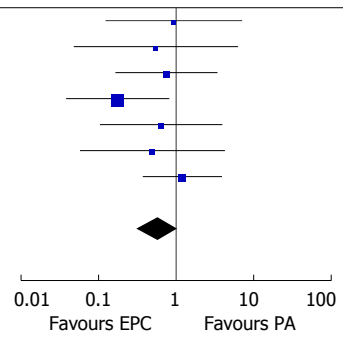


Figure 2 Overall complications. A: Overall complication rates of the two groups are shown in forest plot. The overall complication rates, considering pancreatitis, perforation, bleeding, and cholangitis rates, were 6.2% (30 cases out of 481 patients) in precut group and 6.9% (39 cases out of 558 patients) in persistent attempts group. The pooled analysis did not show any statistically significant difference between the two groups with an OR 0.85 (95%CI: 0.51-1.41); B: The overall complication rates after excluding studies where direct pre-cut was performed. The results were unchanged. EPC: Early pre cut; PA: Persistent attempts.

A

Study or subgroup	EPC Events	EPC Total	PA Events	PA Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Tang 2005	2	32	2	30	6.6%	0.93 [0.12, 7.08]	2005
Zhou 2006	1	43	2	48	6.3%	0.55 [0.05, 6.26]	2006
De Weerth 2006	3	145	4	146	13.4%	0.75 [0.16, 3.41]	2006
Khatibian 2008	2	106	11	112	36.0%	0.18 [0.04, 0.82]	2008
Manes 2008	2	80	3	78	10.2%	0.64 [0.10, 3.94]	2008
Cennamo 2009	1	36	6	110	9.9%	0.50 [0.06, 4.26]	2009
Swan 2013	8	39	6	34	17.5%	1.20 [0.37, 3.90]	2013
Total (95%CI)		481		558	100.0%	0.59 [0.32, 1.07]	
Total events	19		34				

Heterogeneity: χ^2 = 4.14, df = 6 (P = 0.66); I^2 = 0%
Test for overall effect: Z = 1.75 (P = 0.08)



B

Study or subgroup	EPC Events	EPC Total	PA Events	PA Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Tang 2005	2	32	2	30	13.2%	0.93 [0.12, 7.08]	2005
Zhou 2006	1	43	2	48	12.5%	0.55 [0.05, 6.26]	2006
Manes 2008	2	80	3	78	20.1%	0.64 [0.10, 3.94]	2008
Cennamo 2009	1	36	6	110	19.5%	0.50 [0.06, 4.26]	2009
Swan 2013	8	39	6	34	34.6%	1.20 [0.37, 3.90]	2013
Total (95%CI)		230		300	100.0%	0.83 [0.39, 1.78]	
Total events	14		19				

Heterogeneity: χ^2 = 0.81, df = 4 (P = 0.94); I^2 = 0%
Test for overall effect: Z = 0.47 (P = 0.64)

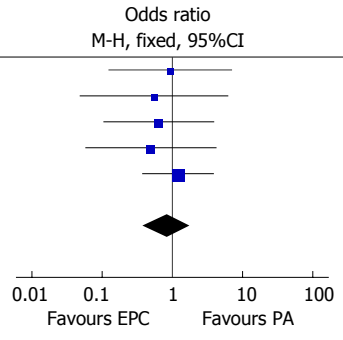


Figure 3 Overall post-endoscopic retrograde cholangiopancreatography pancreatitis. A: Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis rates of the two groups are shown in Forest plot. The risk for post-ERCP pancreatitis was 3.9% (19 cases out of 481 patients) in precut group and 6.1 % (34 cases out of 558 patients) in the persistent attempts group. The pooled analysis did not show any statistically significant difference between the two groups with an OR 0.59 (95%CI: 0.32-1.07); B: The overall post-ERCP pancreatitis rates after excluding studies where direct pre-cut was performed. The results were unchanged. EPC: Early pre cut; PA: Persistent attempts.

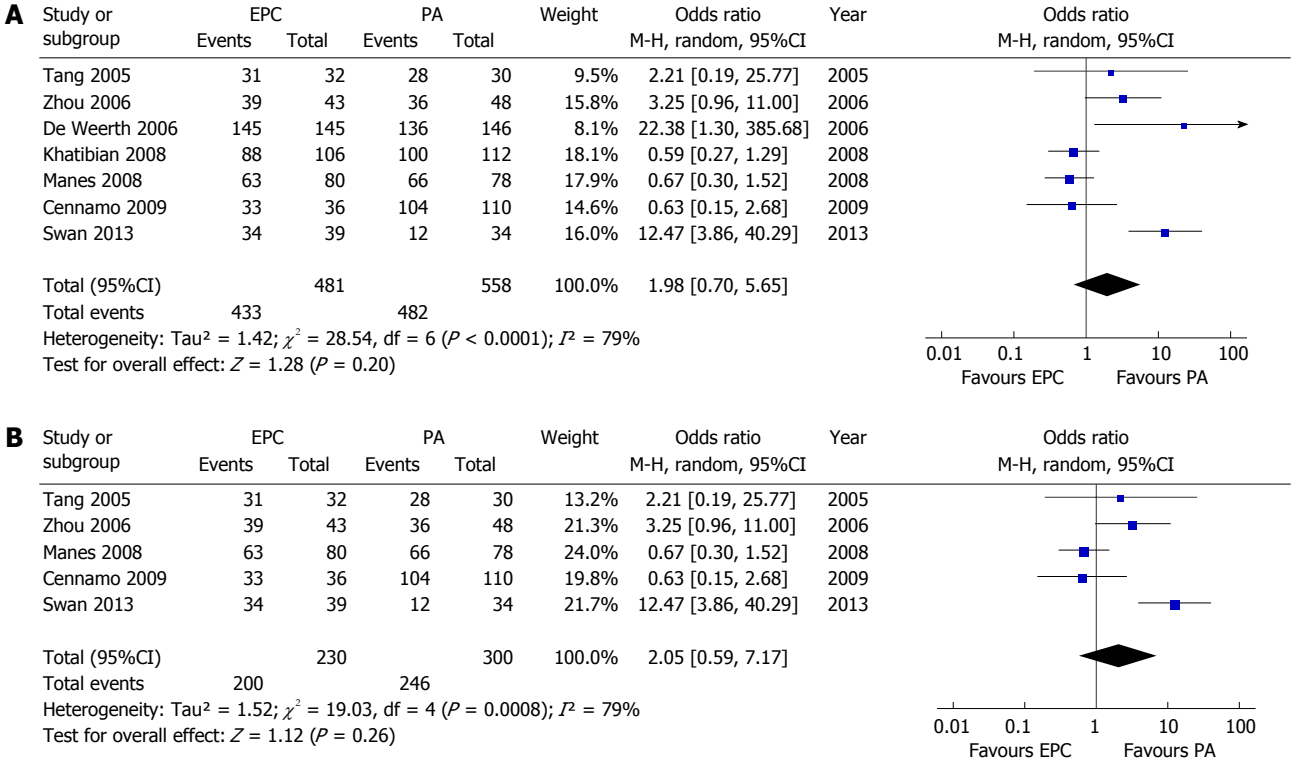


Figure 4 Overall cannulation rates. A: Cannulation rates of the two groups are shown in Forest plot. The overall cannulation rate was found to be 90% in pre-cut sphincterotomy group and 86.3% in persistent attempts group. The pooled analysis did not show any significant difference between the two groups with an OR 1.98 (95%CI: 0.70-5.65); B: The overall cannulation rates after excluding studies where direct pre-cut was performed. The results were unchanged. EPC: Early pre cut; PA: Persistent attempts.

biliary cannulation is achieved in over 90% of patients. In 5%-10% of patients, biliary cannulation is difficult for which various methods have been advocated in the literature. Pre-cut sphincterotomy is a valuable technique to achieve biliary access when conventional techniques fail. However, the timing of this procedure is controversial with some literature suggesting that early use of precut sphincterotomy may be preferable to persistent attempts at cannulation with standard approach. In older literature the use of pre-cut technique has been associated with higher rates of PEP, discouraging its use[9,21].

Past studies assessing the association between PEP and precut sphincterotomy have shown seemingly contradictory results. Two prospective studies[22,23] and one meta-analysis[24], suggested a positive association between precut sphincterotomy and risk of PEP, while in 3 prospective studies there was lack of an independent association between pre-cut sphincterotomy and risk of PEP[10,11,20]. There are multiple case series showing similar complication rates for precut and standard sphincterotomy techniques[25,26]. The discrepancy among these studies may be due to factors such as varying experience among endoscopists, varying precut timing during the procedure, different patient populations and use of prophylactic pancreatic stents. Even among the studies included in this meta-analysis, prophylactic pancreatic stents were used only in one study[14]. Also, non-steroidal anti-inflammatory drugs such as indomethacin were not used in any of the studies included in this analysis. Thus, these results do not entirely mirror the current clinical practice of using either pancreatic stents and/or non-steroidal anti-inflammatory medications when performing difficult biliary cannulation during ERCP.

Our meta-analysis, demonstrated that early pre-cut sphincterotomy does not increase the risk of PEP. In fact, although not statistically significant, there was a trend towards a lower risk of PEP with early use of pre-cut sphincterotomy compared to persistent attempts at cannulation. The possible increased risk of PEP with persistent standard cannulation may be because of mechanical damage to the papilla and the pancreatic sphincter[27-33].

In two studies included in our meta-analysis, pre-cut was performed even without attempts at cannulation with the standard approach[12,18]. The other studies had varying periods of cannulation attempts before randomization, reflecting real clinical practice. After excluding the two studies in which direct pre-cut was performed, the results were unchanged. However the question of when to proceed to pre-cut in patients with difficult biliary cannulation has not been studied in RCTs thus far. The most recent RCT included in this meta-analysis suggested that the risk of PEP increased with more than 6-7 attempts at cannulation suggesting the possible threshold to proceed to pre-cut sphincterotomy[14].

In addition to PEP; bleeding[8] and perforation[9] are other complications associated with precut techniques. In this study the bleeding rate was found to be 1.8% in the

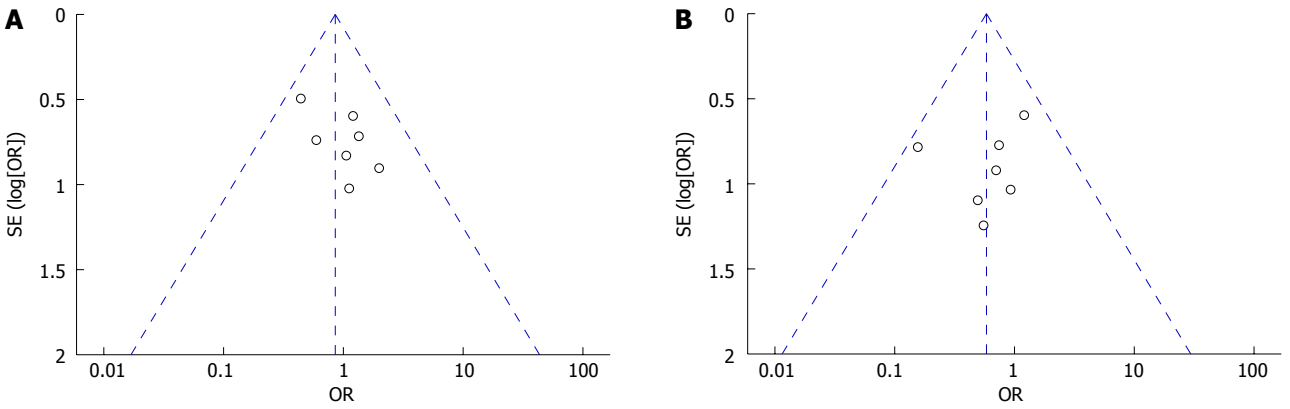


Figure 5 Funnel plot of overall complication and post-endoscopic retrograde cholangiopancreatography pancreatitis rates confirms that publication bias is not a major determinant of pooled diagnostic accuracy in this meta-analysis.

precut group and 0.9% in the persistent attempts group. The perforation rate was found to be 0.4% in the precut group and 0.2% in persistent attempts group. Although we did not detect any statistically significant difference in bleeding and perforation rates between the two groups, the numbers suggest that a larger patient population may have detected possible subtle differences.

The timing of pre-cut remains controversial. Of the seven studies, Tang *et al*[10] study did not include late pre-cut in their analysis. The study by Cennamo *et al*[11] study included early and late pre-cut subgroup and sub-analysis did not showed any difference ($P = 0.25$). The study by de Weerth *et al*[12] included both early and late pre-cut, but the authors that there was no difference in the complications. However, no data was available to do sub-analysis. The other two studies by Manes *et al*[20] and Swan *et al*[14] included patients in early and late pre-cut, but the authors mentioned that subgroup analysis did not show any statistical difference in the post-ERCP complication rates. The other two studies did not separate into early and late pre-cut group for doing a sub-analysis.

The other issue is the use of pancreatic duct (PD) stents one of the studies included in the meta-analysis. In the study by Swan *et al*[14], pancreatic duct (PD) stents were used. There was no significant difference in the use of PD stents between the 2 randomized groups, 15 of 34 (44%) in the standard cannulation arm and 23 of 39 (59%) in the NKS arm. Similarly, there was no statistical difference in the use of PD stents in the standard cannulation group *vs* those in the standard cannulation arm who required crossover to NKS, 5 of 12 (41%) *vs* 10 of 22 (45%). Multivariate analysis of risk factors for PEP showed clearly that PD stent insertion did not affect the results. Hence it is unlikely that use of PD stents affected our results.

It is important to emphasize that precut sphincterotomy, although did not increase the complication rate should be done only for therapeutic ERCP with failed guidewire cannulation. Certain patients are considered to be high-risk for development of PEP. In a meta-analysis, patients with suspected sphincter of Oddi dysfunction (RR = 4.09, 95%CI: 3.37-4.96, $P < 0.001$), female gender (RR 2.23, 95%CI: 1.75-2.84, $P < 0.001$), and those with a previous history of pancreatitis (RR 2.46, 95%CI: 1.93-3.12, $P < 0.001$) were at high risk; additional procedure-related risk factors for PEP were pancreatic sphincterotomy (RR = 2.71, 95%CI: 2.02-3.63, $P < 0.001$) and pancreatic injection (RR = 2.2, 95%CI: 1.6-3.01, $P < 0.001$)[34].

Strengths of this meta-analysis are the inclusion of all RCTs to date. In addition, statistical analysis did not show any significant heterogeneity among the included studies. Furthermore, all included studies reported similar demographic data. However, as all ERCP procedures were done by experienced endoscopists in referral medical centers, the results may not be applicable to community setting practice. Also, the techniques employed for cannulation and precut were different in the included studies. The possible significance of this in altering or modifying the outcomes remains unclear, considering that different techniques may offer different incidence of complications.

To conclude, our study confirms that pre-cut sphincterotomy is a safe and effective strategy when used by experienced biliary endoscopists and does not increase the risk of PEP. However, the exact timing for implementing pre-cut in patients with difficult cannulation remains uncertain and further RCTs employing the time line along with use of pancreatic stents and/or non-steroidal anti-inflammatory medications are required.

COMMENTS

Background

The presumed risks and morbidity associated with needle knife sphincterotomy (NKS) in patients with failed routine cannulation, particularly risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) has discouraged use of this technique in patients with difficult biliary access. The authors sought to perform an updated meta-analysis to study the differences in cannulation rates, PEP and overall complication risk between early pre-cut sphincterotomy and persistent attempts at cannulation, taking the new randomized study into consideration.

Research frontiers

An earlier meta-analysis demonstrated that early precut sphincterotomy reduces PEP risk but not the overall complication rate or cannulation success.

Subsequent to this publication, another RCT has been published.

Innovations and breakthroughs

Based on this meta-analysis, pre-cut sphincterotomy and persistent attempts at cannulation are comparable in terms of overall complication rates.

Applications

Although pre-cut is demonstrated as safe, the exact timing for implementing pre-cut in patients with difficult cannulation remains uncertain and further studies should employ the time line along with use of pancreatic stents and/or non-steroidal anti-inflammatory medications to determine the optimal approach for biliary cannulation.

Terminology

ERCP has been widely used for treatment of a variety of biliary disorders and cannulation of the bile duct remains one of the most important steps for successful therapeutic endoscopy. Precut sphincterotomy, also referred to as NKS, has been advocated in situations where routine biliary cannulation has been unsuccessful.

Peer review

This paper confirms that precut sphincterotomy is not more harmful that persistent attempts of cannulation of the papilla in terms of pancreatitis and other complications. It is well done and the inclusion criteria are correct and well defined.

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META-ANALYSIS

Systematic review of oncological outcomes following laparoscopic *vs* open total mesorectal excision

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Abstract

AIM: To systematically analyze the randomized trials comparing the oncological and clinical effectiveness of laparoscopic total mesorectal excision (LTME) vs open total mesorectal excision (OTME) in the management of rectal cancer.

METHODS: Published randomized, controlled trials comparing the oncological and clinical effectiveness of LTME vs OTME in the management of rectal cancer were retrieved from the standard electronic medical databases. The data of included randomized, controlled trials was extracted and then analyzed according to the principles of meta-analysis using RevMan® statistical software. The combined outcome of the binary variables was expressed as odds ratio (OR) and the combined outcome of the continuous variables was presented in the form of standardized mean difference (SMD).

RESULTS: Data from eleven randomized, controlled trials on 2143 patients were retrieved from the electronic databases. There was a trend towards the higher risk of surgical site infection (OR = 0.66; 95%CI: 0.44-1.00; z = 1.94; $P < 0.05$), higher risk of incomplete total mesorectal resection (OR = 0.62; 95%CI: 0.43-0.91; z = 2.49; $P < 0.01$) and prolonged length of hospital stay (SMD, -1.59; 95%CI: -0.86--0.25; z = 4.22; $P < 0.00001$) following OTME. However, the oncological outcomes like number of harvested lymph nodes, tumour recurrence and risk of positive resection margins were statistically similar in both groups. In addition, the clinical outcomes such as operative complications, anastomotic leak and all-cause mortality were comparable between both approaches of mesorectal excision.

CONCLUSION: LTME appears to have clinically and oncologically measurable advantages over OTME in patients with primary rectal cancer in both short term and long term follow ups.

Key words: Total mesorectal excision; Anterior resection; Abdominoperineal resection; Rectal cancer; Oncological outcomes

Core tip: Based upon the findings of this systematic review of eleven randomized trial on 2143 patients of rectal cancer, there is a higher risk of surgical site infection, higher risk of incomplete total mesorectal resection and prolonged length of hospital stay following open total mesorectal excision (OTME) compared to laparoscopic total mesorectal excision (LTME). The number of harvested lymph nodes, tumour recurrence and risk of positive resection margins were statistically similar in both groups. In addition, the operative complications, anastomotic leak and mortality were compa-

rable between LTME and OTME. LTME appears to have clinically and oncologically measurable advantages over OTME in patients with primary resectable rectal cancer.

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INTRODUCTION

Colorectal cancer is one of the major causes of mortality among western population[1,2]. Radical resection of the rectum in the form of anterior resection and abdominoperineal resection has been advocated for many decades to achieve highest level of oncological clearance and overall survival[3-8]. The introduction of total mesorectal excision in the management of rectal cancer has also enhanced survival and reduced the risk of local recurrence[9-14] because it achieves complete excision of the rectum together with its lymphatics and lymph nodes. Therefore, total mesorectal excision has become gold standard surgical strategy to treat rectal malignancies[10,11]. Laparoscopic total mesorectal excision (LTME) offers several advantages over conventional and orthodox open total mesorectal excision (OTME) such as reduced blood loss, faster recovery, reduced postoperative pain score, early feeding, early return to normal activities and a reduced risk of postoperative complications[12-16]. However, these advantages of LTME can only be availed optimally by colorectal surgeons when its oncological viability is proven on scientific grounds. One would assume that LTME for rectal cancer should offer survival and recurrence similar to OTME[17-19]. In addition, several studies have also reported the concerns towards LTME requiring longer duration of operation, needing extensive learning curve for colorectal surgeons, particularly junior colorectal trainees and cost implications of the procedure[20,21]. Aforementioned three limitations of LTME can be offset if its oncological and clinical adequacy matches the OTME. The objective of this article is to explore the oncological safety and clinical effectiveness of the LTME comparing to OTME based upon the principles of meta-analysis.

MATERIALS AND METHODS

Electronic data sources and their search planning

In order to obtain pertinent studies, a search of common medical electronic databases such as MEDLINE, EMBASE, and the Cochrane library for randomized, controlled trials was conducted and screened according to PRIMSA flow chart (Figure 1). The MeSH terms published in the Medline library relevant to the oncological and clinical outcomes following LTME or OTME were used to hit upon the relevant trials. No limits for language, gender, sample size and place of study origin were entered for the search in the database search engine. Boolean operators (AND, OR = NOT) were additionally used to narrow and widen the results of potentially usable studies. The titles of the published articles from the search results were examined closely and determined to be suitable for potential inclusion into this review article. The reference list from selected articles was also examined as a further search tool to discover additional trials.

Selection criteria for included trials

For inclusion in this meta-analysis, a study had to fulfill the following criteria: (1) randomized, controlled trial; (2) comparison between LTME and OTME; (3) evaluation of a well-defined primary outcome; (4) main outcome measures reported preferably as an intention-to-treat (ITT) analysis; and (5) trials on surgical patients those have endoscopically and histologically proven rectal cancer.

Data abstraction from included trials

Two independent reviewers using a predefined meta-analysis form abstracted relevant data of oncological and clinical outcomes following LTME and OTME from each study which resulted in high and satisfactory interobserver agreement. The extracted data contained name of the publishing authors, title of the published study, journal in which the study was published, country and year of the study, intervention protocol in the both limbs of the trial, method by which LTME and OTME was performed, testing sample size (with sex differentiation if applicable), the number of patients receiving each regimen and within the group the number of patients who succeeded and the number of patients who failed the allocated treatment, the patient compliance rate in each group, the number of patients reporting complications and the number of patients with absence of complications in each arm of the trial. After completing the data abstraction the two independent reviewers discussed the data related results and, if discrepancies were present, a consensus was reached.

Statistical analysis

The software package RevMan 5.2[22,23], provided by the Cochrane Collaboration, was used for the statistical analysis. The odds ratio (OR) with a 95%CI was calculated for binary data, and the standardized mean difference (SMD) with a 95%CI was calculated for continuous variables. The random-effects model[24,25] was used to calculate the combined outcomes of both binary and continuous variables. Heterogeneity was explored using the χ^2 test, with significance set at $P < 0.05$, and was quantified[26] using I^2, with a maximum value of 30 percent identifying low heterogeneity[26]. The Mantel-Haenszel method was used for the calculation of OR under the random effect models[27]. In a sensitivity analysis, 0.5 was added to each cell frequency for trials in which no event occurred in either

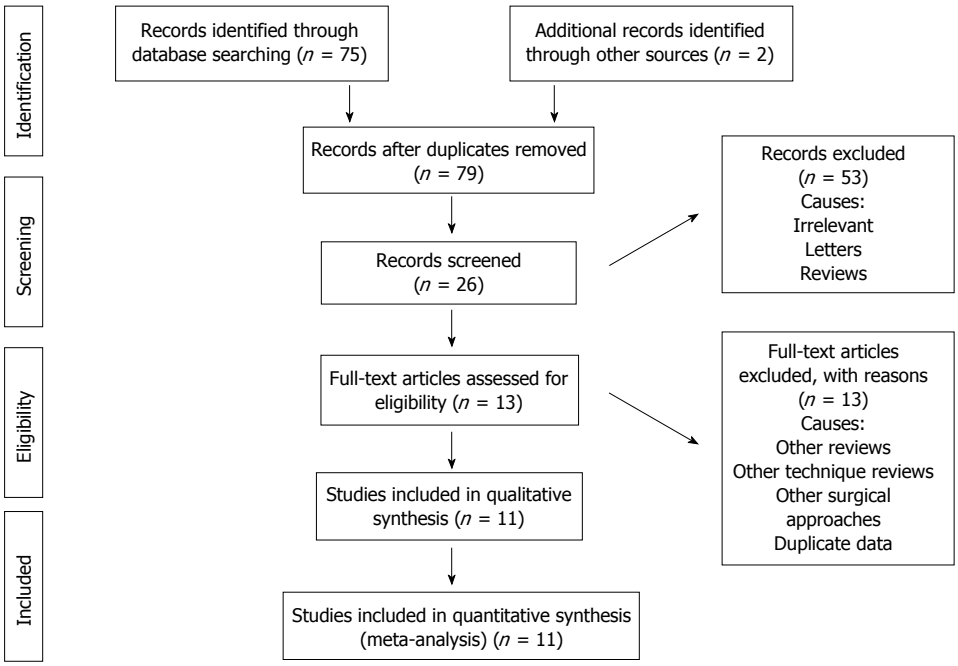


Figure 1 PRISMA flow diagram.

the treatment or control group, according to the method recommended by Deeks *et al*[28]. If the standard deviation was not available, then it was calculated according to the guidelines of the Cochrane Collaboration[22]. This process involved assumptions that both groups had the same variance, which may not have been true, and variance was either estimated from the range or from the *P*-value. The estimate of the difference between both techniques was pooled, depending upon the effect weights in results determined by each trial estimate variance. A forest plot was used for the graphical display of the results. The square around the estimate stood for the accuracy of the estimation (sample size), and the horizontal line represented the 95%CI. The methodological quality of the randomized, controlled trials was assessed using the published guidelines of Jaddad *et al*[29] and Chalmers *et al*[30]. Based on the quality of the included randomized, controlled trials, the strength and summary of the evidence was further evaluated by GradePro®[31], a tool provided by the Cochrane Collaboration.

Outcomes

Incidence of complete TME was analysed as primary endpoint in this study. Secondary endpoints included circumferential resection margin (CRM) positivity, number of harvested lymph nodes, mortality, morbidity, anastomotic leak, surgical site infection and length of hospital stay.

RESULTS

Eleven randomized, controlled trials encompassing 2143 patients[32-42] were retrieved from the electronic databases. There were 1189 patients in the LTME group and 954 patients in the OTME group. The characteristics of the included trials are given in Table 1. The salient features and treatment protocols adopted in the included trials are given in Table 2. We used the data from one publication only from two published articles[35,36] of same randomized, controlled trial in order to avoid the duplication of data.

Methodological quality of included studies

Based upon the published guidelines of Jaddad *et al*[29] and Chalmers *et al*[30] the quality of majority of included randomized, controlled trials[33,35-41] was considered good. Only three[32,34,42] included trials were scored of low quality due to the absence of adequate randomisation technique, power calculations, blinding, adequate concealment process and lack of intention-to-treat analysis. Based on the quality of included trials, the strength and summary of the evidence analyzed on GradePro®[31] is given in Figure 2. The reported quality variables of included trials are given in Table 3.

Risk of incomplete total mesorectal excision

There was no heterogeneity [$Tau^2 = 0.00$, $\chi^2 = 2.41$, $\gamma = 3$, ($P = 0.49$); $I^2 = 0\%$] among included studies. In the random effects model (OR = 0.62; 95%CI: 0.43-0.91; z = 2.49; $P < 0.01$; Figure 3A), the risk of incomplete total mesorectal excision was higher following OTME compared to LTME.

Risk of positive circumferential resection margins

There was no heterogeneity [$Tau^2 = 0.0$, $\chi^2 = 1.80$, $\gamma = 7$, ($P = 0.97$); $I^2 = 0\%$] among included studies. In the random effects model (OR = 0.98; 95%CI: 0.63, 1.51; z = 0.10; $P = 0.71$; Figure 3B), the risk of positive circum-

Table 1 Characteristics of included trials

Ref.	Year	Country	Age (yr)	Gender (M:F)	Follow up (mo)	Rectal cancer details	Procedure
Araujo *et al*[32]	2003	Brazil				Lower rectal cancer with neoadjuvant chemoradiotherapy	Abdominoperineal resection
LTME			59.1	9:4	47.2		
OTME			56.4	10:5	47.2		
Baraga *et al*[33]	2007	Italy				Adenocarcinoma of the rectum suitable for resection with neoadjuvant chemoradiotherapy	Anterior resection and Abdominoperineal resection
LTME			62.8 ± 12.6	55:28	53.6		
OTME			65.3 ± 10.3	64:21			
Gong *et al*[34]	2012	China				Lower and mid rectal adenocarcinoma without neoadjuvant chemoradiotherapy	Anterior resection and Abdominoperineal resection
LTME			58.4 ± 13.6	1.3:1	21 (9-56)		
OTME			59.6 ± 9.4	1.29:1			
Guillou *et al*[35]	2005	United				Adenocarcinoma of left colon and rectum	Anterior resection and Abdominoperineal resection
LTME		Kingdom	69 ± 11	44% female	3		
OTME			69 ± 12	46% female	3		
Jayne *et al*[36]	2007	United				Adenocarcinoma of left colon and rectum	Anterior resection and Abdominoperineal resection
LTME		Kingdom	69 ± 11	44% female	36.5		
OTME			69 ± 12	46% female	36.5		
Kang *et al*[37]	2010	South				Lower and mid rectal adenocarcinoma with neoadjuvant chemoradiotherapy	Anterior resection and Abdominoperineal resection
LTME		Korea	57.8 ± 11.1	110:60	3		
OTME			59.1 ± 9.9	110:60	3		
Lujan *et al*[38]	2009	Spain				Upper rectal adenocarcinoma Mid or low rectal adenocarcinoma cT3N0-2 stage Preoperative chemoradiotherapy	Anterior resection and Abdominoperineal resection
LTME			67.8 ± 12.9	62:39	32.8		
OTME			66 ± 9.9	64:39	34.1		
Ng *et al*[39]	2008	Hong				Lower rectal cancer within 5 cm of the anal verge	Abdominoperineal resection
LTME		Kong	63.7 ± 11.8	31:20	90.1		
OTME			63.5 ± 12.6	30:18	87.2		
Ng *et al*[40]	2009	Hong				Upper rectal adenocarcinoma Preoperative chemoradiotherapy	Anterior resection
LTME		Kong	66.5 ± 11.9	37:39	112.5		
OTME			65.7 ± 12	48:29	108.8		
Ng *et al*[41]	2013	Hong				Rectal adenocarcinoma located between 5 and 12 cm from the anal verge. None of the included patient had neoadjuvant treatment	Sphincter sparing total mesorectal excision
LTME		Kong	60.2 ± 11.3	24:16	84.6		
OTME			62.1 ± 12.6	22:18	92.7		
Zhou *et al*[42]	2004	China				Low rectal adenocarcinoma Intraperitoneal and 1.5 to 8 cm from the dentate line Dukes D with local infiltration Anal sphincter sparing	Anterior resection
LTME			26-85(44)	43:46			
OTME			30-81(45)	46:36	1-16		

LTME: Laparoscopic total mesorectal excision; OTME: Open total mesorectal excision; M: Male; F: Female.

ferential resection margins was similar following both approaches.

Number of harvested lymph nodes

There was significant heterogeneity [$Tau^2 = 0.12$, $\chi^2 = 48.61$, $\gamma = 8$, ($P > 0.00001$); $I^2 = 84\%$] among included studies. In the random effects model (SMD, -0.14; 95%CI: -0.40-0.12; z = 1.08; $P < 0.28$; Figure 3C), the number of harvested lymph nodes following both procedures was statistically similar.

Recurrence

There was no heterogeneity [$Tau^2 = 0.00$, $\chi^2 = 4.57$, $\gamma = 7$, ($P = 0.71$); $I^2 = 0\%$] among included studies. In the random effects model (OR = 0.82; 95%CI: 0.59-1.15; z = 1.16; $P = 0.24$; Figure 3D), the risk of rectal cancer recurrence was similar between both types of excisions.

Duration of hospital stay

There was significant heterogeneity [$Tau^2 = 0.21$, $\chi^2 = 82.18$, $\gamma = 9$, ($P < 0.00001$); $I^2 = 89\%$] among included studies. In the random effects model (SMD, -1.59; 95%CI: -0.86--0.25; z = 4.22; $P < 0.00001$; Figure 3E), the length of hospital stay was shorter following LTME compared to OTME.

Short term and long term operative complications

There was significant heterogeneity [$Tau^2 = 0.30$, $\chi^2 = 28.55$, $\gamma = 9$, ($P < 0.0008$); $I^2 = 68\%$] among included studies. In the random effects model (OR = 0.69; 95%CI: 0.43, 1.08; z = 1.62; $P = 0.11$; Figure 3F), the incidence of complications was similar following both approaches of rectal cancer resection.

Overall mortality

There was no heterogeneity [$Tau^2 = 0.00$, $\chi^2 = 0.45$, $\gamma = 3$, ($P = 0.93$); $I^2 = 0\%$] among included studies. In the random effects model (OR = 0.70; 95%CI: 0.41-1.18; z = 1.33; $P = 0.18$; Figure 3G), the incidence of overall mortality was similar following LTME and OTME.

Anastomosis leak

There was no heterogeneity [$Tau^2 = 0.00$, $\chi^2 = 6.18$, $\gamma = 7$, ($P = 0.52$); $I^2 = 0\%$] among included studies. In the

Table 2 Treatment protocol adopted in included trials

Ref.	LTME group	OTME group
Araujo *et al*[32]	4 × 10/11 mm ports were used with some variations Trendelenburg position Harmonic scalpel for dissection Lateral to medial dissection Endoscopic stapler for inferior mesenteric pedicle division Colonic division by endostapler Standard technique of colostomy construction Standard perineal phase, dissection and closure	Procedure protocol was not reported
Baraga *et al*[33]	Intracorporeal vascular pedicle division, rectal mobilization and division, and anastomosis Anastomosis by Knight-Griffen technique Selective defunctioning stoma placement	Procedure protocol was not reported Selective defunctioning stoma placement
Gong *et al*[34]	4 ports were used with some variations Medial to lateral dissection Clips to secure inferior mesenteric pedicle Rectal division by endostapler Standard technique of colostomy construction Standard perineal phase, dissection and closure	Standard open TME Sphincter preserving surgery in both groups in selective patients No defunctioning stoma in both groups
Guillou *et al*[35]	Detailed procedure protocol was not reported	Detailed procedure protocol was not reported
Jayne *et al*[36]	3 yr results of Guillou *et al*[35] Detailed procedure protocol was not reported	3 yr results of Guillou *et al*[35] Detailed procedure protocol was not reported
Kang *et al*[37]	Six weeks after completion of chemoradiotherapy 5 ports were used Clips to secure inferior mesenteric pedicle Splenic flexure was mobilized in all patients Harmonic scalpel or diathermy for dissection Rectal division by endostapler Colorectal anastomosis by double staple technique or by trans-anal suture All patients had defunctioning stoma	Detailed procedure protocol was not reported Sphincter preservation in selective patients in both groups
Lujan *et al*[38]	4 ports were used Stapled side to end colorectal or colo-anal hand sewn anastomosis Selective defunctioning stoma placement	Lloyd-Davis position and midline laparotomy Stapled side to end colorectal or colo-anal hand sewn anastomosis Sphincter preservation in selective patients in both groups Selective defunctioning stoma placement
Ng *et al*[39]	4 or 5 ports were used Staplers for vascular pedicle and bowel transection Standard perineal resection	Standard open abdominoperineal resection
Ng *et al*[40]	Protocol of the laparoscopic resection technique was not reported	Protocol of the open resection technique was not reported
Ng *et al*[41]	Lateral to medial mobilization Endostapler for rectal and vascular pedicle transection Electrocautry was used to dissect through "Holy plane" for total mesorectal resection Splenic flexure mobilization in selective patients Anastomosis by double stapling technique Defunctioning stoma in selective patients	Protocol of the open resection technique was not reported
Zhou *et al*[42]	Lithotomy position with head down tilt Laparoscopy technique was not reported Intracorporeal anastomosis Endostapler for vascular and rectal transactions Harmonic scalpel was used for dissection No defunctioning stoma	Standard open total mesorectal excision previously published by Heald *et al*[10,11] Electrocautry was used for hemostasis No defunctioning stoma

TME: Total mesorectal excision; LTME: Laparoscopic total mesorectal excision; OTME: Open total mesorectal excision.

random effects model (OR = 0.92; 95%CI: 0.56-1.50; z = 0.33; P = 0.74; Figure 3H), the risk of colorectal anastomotic dehiscence was similar following both approaches.

Surgical site infection

There was significant no heterogeneity [Tau^2 = 0.07, χ^2 = 10.61, γ = 9, (P = 0.30); I^2 = 15%] among included studies. In the random effects model (OR = 0.66; 95%CI: 0.44-1.00; z = 1.94; $P < 0.05$; Figure 3I), the risk of surgical site infection was higher following OTME compared to LTME.

DISCUSSION

Based upon the findings of this largest ever systematic review of eleven randomized, controlled trial on 2143

All variables in LTME *vs* OTME for [health problem]

Patient or population: patients with [healith problem]

Settings:

Intervention: All variables in LTME *vs* OTME

Outcomes	Illustrative comparative risks[1] (95%CI) Assumed risk Control	 Corresponding risk All variables in LTME *vs* OTME	Relative effect (95%CI)	No of participants (students)	Quality of the evidence (GRADE)	Comments
Incidence of incomplete TME OR Follow-up: 3-12 mo	Study population 85 per 1000 Moderate 0 per 1000	54 per 1000 (38 to 78) 0 per 1000 (0 to 0)	OR = 0.62 (0.43 to 0.91)	1762 (10 studies)	Moderate	
Incidence of CRM positivity OR Follow-up: 3-112 mo	Study population 55 per 1000 Moderate 35 per 1000	54 per 1000 (36 to 81) 34 per 1000 (22 to 52)	OR = 0.98 (0.63 to 1.51)	1563 (8 studies)	Moderate	
Number of harvested lymph nodes Standardized mean difference Follow-up: 3-112 mo		The mean number of harvested lymph nodes in the intervention groups was 0.14 standard deviations lower (0.4 lower to 0.12 higher)		1633 (9 studies)	Moderate	SMD -0.14 (-0.4 to 0.12)
Recurrence OR Follow-up: 3-112 mo	Study population 131 per 1000 Moderate 133 per 1000	110 per 1000 (82 to 148) 112 per 1000 (83 to 150)	OR = 0.82 (0.59 to 1.15)	1422 (9 studies)	Moderate	
Length of stay Standardized mean difference Follow-up: 3-112 mo		The mean length of stay in the intervention groups was 0.55 standard deviation lower (0.86 ti 0.25 lower)		1762 (10 studies)	Moderate	SMD -0.55 (-0.86 to -0.25)
Short and long term complications OR Follow-up: 3-112 mo	Study population 430 per 1000 Moderate 503 per 1000	342 per 1000 (245 to 449) 411 per 1000 (303 to 522)	OR = 0.69 (0.43 to 1.08)	1762 (10 studies)	Moderate	
All cause mortality OR Follow-up: 3-112 mo	Study population 41 per 1000 Moderate 430 per 1000	29 per 1000 (17 to 48) 430 per 1000 (0 to 0)	OR = 0.7 (0.41 to 1.18)	1762 (10 studies)	Moderate	
Anastomosis leak rate OR Follow-up: 3-112 mo	Study population 46 per 1000 Moderate 34 per 1000	42 per 1000 (26 to 67) 31 per 1000 (19 to 50)	OR = 0.92 (0.56 to 1.5)	1732 (9 studies)	Moderate	
Surgical site infection OR Follow-up: 3-112 mo	Study population 99 per 1000 Moderate 117 per 1000	68 per 1000 (46 to 99) 80 per 1000 (55 to 117)	OR = 0.66 (0.44 to 1)	1762 (10 studies)	Moderate[2]	

[1]The basis for the assumed risk (*e.g.*, the median control group risk across studies) is provided in footnotes.
The corresponding risk (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI)
GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
[2]No explanation was provided.

Figure 2 Strength and summary of the evidence analysed on GradePro®.

Table 3 Quality variables reported in the included trials

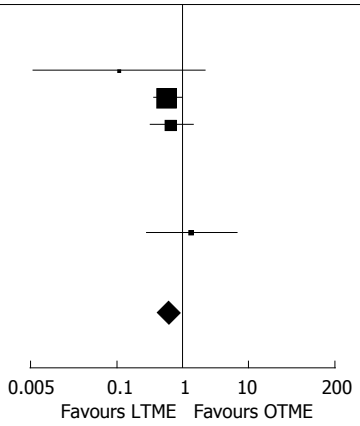
Ref.	Randomization	Power calculations	ITT	Blinding	Concealment
Araujo *et al*[32]	Not reported	Not reported	Not reported	Not reported	Not reported
Baraga *et al*[33]	Computer generated	Yes	Yes	Yes	Sealed blinded envelops
Gong *et al*[34]	Not reported	Not reported	Not reported	Not reported	Not reported
Guillou *et al*[35]	Random allocation with 2 to 1 ratio	Yes	Yes	Not reported	Allocation communicated by telephone
Jayne *et al*[36]	Random allocation with 2 to 1 ratio	Yes	Yes	Not reported	Allocation communicated by telephone
Kang *et al*[37]	Computer generated with block permutation	Yes	Yes	Yes	Allocation communicated by telephone
Lujan *et al*[38]	Computer generated	Yes	Yes	Yes	Sealed blinded envelops
Ng *et al*[39]	Computer generated random sequence	Yes	Yes	Yes	Concealed by theatre coordinator
Ng *et al*[40]	Computer generated	Yes	Yes	Not reported	Not reported
Ng *et al*[41]	Computer generated random sequence	Yes	Yes	Yes	Concealed by theatre coordinator
Zhou *et al*[42]	Not reported	Not reported	Not reported	Not reported	Not reported

ITT: Intention-to-treat.

A

Study or subgroup	LTME Events	LTME Total	OTME Events	OTME Total	Weight	Odds ratio M-H, random, 95%CI
Araujo 2003	0	13	0	15		Not estimable
Baraga 2007	0	83	0	85		Not estimable
Gong 2012	0	67	4	71	1.7%	0.11 [0.01, 2.10]
Guillou 2005	58	253	43	128	64.8%	0.59 [0.37, 0.94]
Kang 2010	14	170	20	170	27.7%	0.67 [0.33, 1.38]
Lujan 2009	0	101	0	103		Not estimable
Ng 2008	0	51	0	48		Not estimable
Ng 2009	0	76	0	77		Not estimable
Ng 2013	4	40	3	40	5.8%	1.37 [0.29, 6.56]
Zhou 2004	0	82	0	89		Not estimable
Total (95%CI)		936		826	100.0%	0.62 [0.43, 0.91]
Total events	76		70			

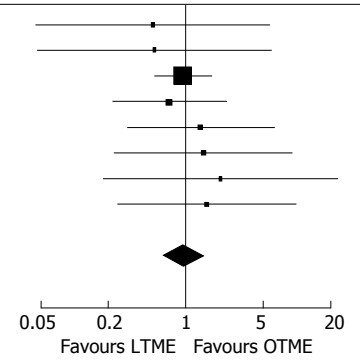
Heterogeneity: Tau^2 = 0.00; χ^2 = 2.41; df = 3 (P = 0.49); I^2 = 0%
Test for overall effect: Z = 2.45 (P = 0.01)



B

Study or subgroup	LTME Events	LTME Total	OTME Events	OTME Total	Weight	Odds ratio M-H, random, 95%CI
Baraga 2007	1	83	2	85	3.2%	0.51 [0.05, 5.69]
Gong 2012	1	67	2	71	3.2%	0.52 [0.05, 5.90]
Guillou 2005	40	253	21	128	57.0%	0.96 [0.54, 1.70]
Kang 2010	5	170	7	170	13.9%	0.71 [0.22, 2.71]
Lujan 2009	4	101	3	103	8.2%	1.37 [0.30, 6,30]
Ng 2008	3	51	2	48	5.6%	1.44 [0.23, 9.00]
Ng 2009	2	76	1	77	3.2%	2.05 [0.18, 23.14]
Ng 2013	3	40	2	40	5.6%	1.54 [0.24, 9.75]
Total (95%CI)		841		722	100.0%	0.98 [0.63, 1.51]
Total events	59		40			

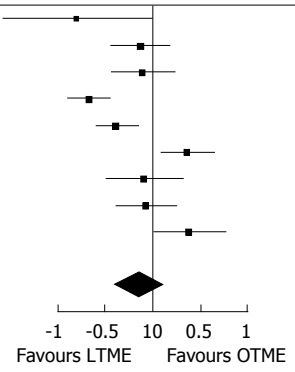
Heterogeneity: Tau^2 = 0.00; χ^2 = 1.80; df = 7 (P = 0.97); I^2 = 0%
Test for overall effect: Z = 0.10 (P = 0.92)



C

Study or subgroup	LTME Mean	LTME SD	LTME Total	OTME Mean	OTME SD	OTME Total	Weight	Std. mean difference IV, random, 95%CI
Araujo 2003	5.5	7.8	13	11.9	7.8	15	6.2%	-0.80 [-1.57, -0.02]
Baraga 2007	12.7	7.3	83	13.6	6.9	85	11.8%	-0.13 [-0.43, 0.18]
Gong 2012	20.3	8.3	67	21.1	6.7	71	11.4%	-0.11 [-0.44, 0.23]
Guillou 2005	12	2.25	253	13.5	2.25	128	12.8%	-0.38 [-0.59, -0.17]
Kang 2010	17	2.5	170	18	2.75	170	12.8%	-0.38 [-0.59, -0.17]
Lujan 2009	13.63	6.26	101	11.57	5.1	103	12.1%	0.36 [0.08, 0.64]
Ng 2008	12.4	6.7	51	13	7	48	10.6%	-0.09 [-0.48, 0.31]
Ng 2009	11.5	7.9	76	12	7	77	11.6%	-0.07 [-0.38, 0.25]
Ng 2013	17.7	8.4	82	14.8	5.6	40	10.8%	0.38 [-0.00, 0.76]
Total (95%CI)			896			737	100.0%	-0.14 [-0.40, 0.12]

Heterogeneity: Tau^2 = 0.12; χ^2 = 48.61; df = 8 (P < 0.00001); I^2 = 84%
Test for overall effect: Z = 1.08 (P = 0.28)

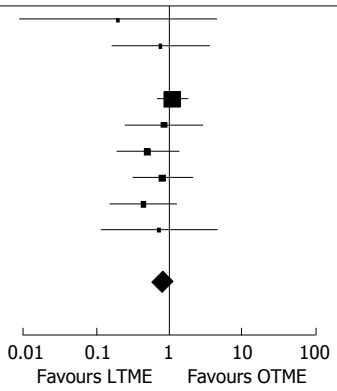


D

Study or subgroup	LTME Events	LTME Total	OTME Events	OTME Total	Weight	Odds ratio M-H, random, 95%CI
Araujo 2003	0	13	2	15	1.1%	0.20 [0.01, 4.57]
Baraga 2007	3	83	4	85	4.8%	0.76 [0.16, 3.50]
Gong 2012	0	67	0	71		Not estimable
Guillou 2005	72	253	34	128	49.0%	1.10 [0.68, 1.77]
Lujan 2009	5	101	6	103	7.5%	0.84 [0.25, 2.85]
Ng 2008	8	51	13	48	11.5%	0.50 [0.19, 1.34]
Ng 2009	9	76	11	77	12.5%	0.81 [0.31, 2.07]
Ng 2013	7	40	13	40	10.1%	0.44 [0.15, 1.26]
Zhou 2004	2	82	3	89	3.4%	0.72 [0.12, 4.40]
Total (95%CI)		766		656	100.0%	0.82 [0.59, 1.15]
Total events	106		86			

Heterogeneity: Tau^2 = 0.00; χ^2 = 4.57; df = 7 (P = 0.71); I^2 = 0%

Test for overall effect: Z = 1.16 (P = 0.24)

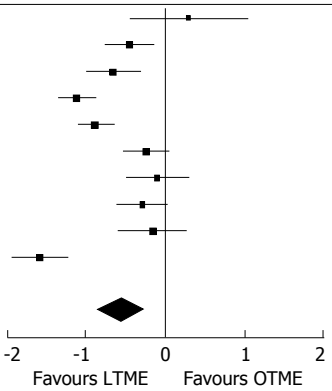


E

Study or subgroup	LTME Mean	LTME SD	LTME Total	OTME Mean	OTME SD	OTME Total	Weight	Std. Mean Difference IV, random, 95%CI
Araujo 2003	10.5	3.2	13	9.5	3.2	15	6.9%	0.30 [-0.44, 1.05]
Baraga 2007	10	4.9	83	13.6	10	85	10.5%	-0.45 [-0.76, -0.15]
Gong 2012	10.4	4.3	67	13.8	5.9	71	10.2%	-0.65, [-0.99, -0.31]
Guillou 2005	11	1.5	253	13	2.25	128	11.0%	-1.12 [-1.34, -0.89]
Kang 2010	8	1.25	170	9	1	170	11.0%	-0.88 [-1.10, -0.66]
Lujan 2009	8.2	7.3	101	9.9	6.8	103	10.7%	-0.24 [-0.52, 0.04]
Ng 2008	10.8	5.5	51	11.5	8.25	48	9.8%	-0.10 [-0.49, 0.29]
Ng 2009	8.4	5	76	10	6	77	10.4%	-0.29 [-0.61, 0.03]
Ng 2013	10.5	4.5	40	15	40.25	40	9.4%	-0.16 [-0.59, 0.28]
Zhou 2004	8.1	3.1	82	13.3	3.4	89	10.2%	-1.59 [-1.93, -1.24]
Total (95%CI)			936			826	100.0%	-0.55 [-0.86, -0.25]

Heterogeneity: Tau^2 = 0.21; χ^2 = 82.18; df = 9 (P < 0.00001); I^2 = 89%

Test for overall effect: Z = 3.53 (P = 0.0004)

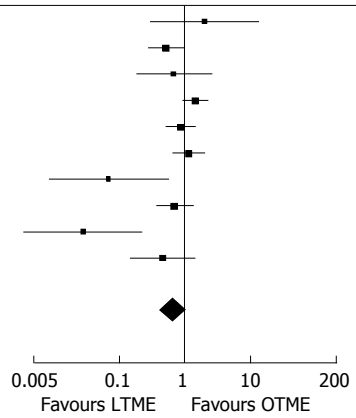


F

Study or subgroup	LTME Events	LTME Total	OTME Events	OTME Total	Weight	Odds ratio M-H, random, 95%CI
Araujo 2003	11	13	11	15	4.4%	2.00 [0.30, 13.26]
Baraga 2007	29	83	43	85	13.5%	0.52 [0.28, 0.98]
Gong 2012	4	67	6	71	7.3%	0.69 [0.19, 2.55]
Guillou 2005	150	253	64	128	15.6%	1.46 [0.95, 2.23]
Kang 2010	45	170	50	170	15.1%	0.86 [0.54, 1.39]
Lujan 2009	47	101	44	103	14.3%	1.17 [0.67, 2.03]
Ng 2008	39	51	47	48	3.8%	0.07 [0.01, 0.56]
Ng 2009	33	76	40	77	13.4%	0.71 [0.38, 1.34]
Ng 2013	21	40	39	40	3.8%	0.03 [0.00, 0.23]
Zhou 2004	5	82	11	89	8.8%	0.46 [0.15, 1.39]
Total (95%CI)		936		826	100.0%	0.69 [0.43, 1.08]
Total events	384		355			

Heterogeneity: Tau^2 = 0.30; χ^2 = 28.55; df = 9 (P = 0.0008); I^2 = 68%

Test for overall effect: Z = 1.62 (P = 0.11)

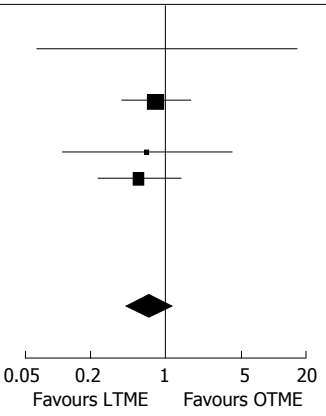


G

Study or subgroup	LTME Events	LTME Total	OTME Events	OTME Total	Weight	Odds ratio M-H, random, 95%CI
Araujo 2003	0	13	0	15		Not estimable
Baraga 2007	1	83	1	85	3.5%	1.02 [0.06, 16.65]
Gong 2012	0	67	0	71		Not estimable
Guillou 2005	21	253	13	128	52.2%	0.80 [0.39, 1.66]
Kang 2010	0	170	0	170		Not estimable
Lujan 2009	2	101	3	103	8.4%	0.67 [0.11, 4.12]
Ng 2008	12	51	17	48	35.9%	0.56 [0.23, 1.35]
Ng 2009	0	76	0	77		Not estimable
Ng 2013	0	40	0	40		Not estimable
Zhou 2004	0	82	0	89		Not estimable
Total (95%CI)		936		826	100.0%	0.70 [0.41, 1.18]
Total events	36		34			

Heterogeneity: Tau^2 = 0.00; χ^2 = 0.45; df = 3 (P = 0.93); I^2 = 0%

Test for overall effect: Z = 1.33 (P = 0.18)



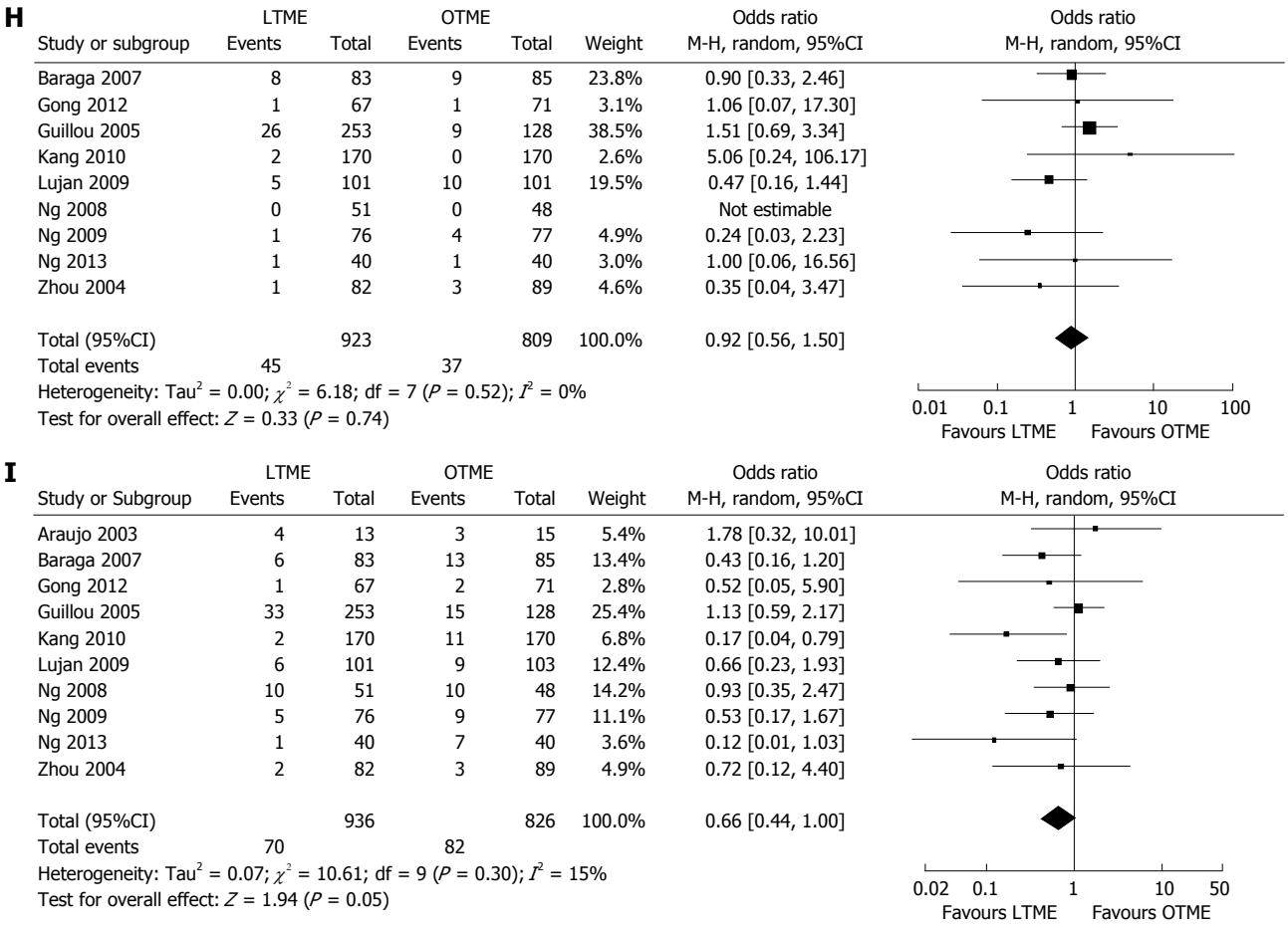


Figure 3 Forest plot. A: Of risk of incomplete total mesorectal excision following laparoscopic total mesorectal excision (LTME) *vs* open total mesorectal excision (OTME) for rectal cancer. Odds ratios are shown with 95%CIs; B: Of risk of risk of circumferential resection margin positivity following LTME *vs* OTME for rectal cancer. Odds ratios are shown with 95%CIs; C: Of number of harvested lymph nodes following LTME *vs* OTME for rectal cancer. Standardized mean differences are shown with 95%CIs; D: Of recurrence following LTME *vs* OTME for rectal cancer. Odds ratios are shown with 95%CIs; E: Of length of stay following LTME *vs* OTME for rectal cancer. Standardized mean differences are shown with 95%CIs; F: Of complications following LTME *vs* OTME for rectal cancer. Odds ratios are shown with 95%CIs; G: Of all-cause mortality following LTME *vs* OTME for rectal cancer. Odds ratios are shown with 95%CIs; H: Of anastomosis leak following LTME *vs* OTME for rectal cancer. Odds ratios are shown with 95%CIs; I: Of surgical site infection following LTME *vs* OTME for rectal cancer. Odds ratios are shown with 95%CIs.

patients of rectal cancer, there is a higher risk of surgical site infection, higher risk of incomplete total mesorectal resection and prolonged length of hospital stay following OTME compared to LTME. The oncological outcomes like the number of harvested lymph nodes, incidence of tumour recurrence and risk of positive resection margins were statistically similar in both groups. In addition, the clinical outcomes such as operative complications, anastomotic leak and all-cause mortality were comparable between both approaches of the mesorectal excision. LTME appears to have clinically and oncologically measurable advantages over OTME in patients with primary resectable rectal cancer in both short term and long term follow ups.

The findings of this article are consistent with previously published Cochrane review and a meta-analysis[43,44]. Majority of the studies in the Cochrane review[44] were non-randomized, trials and therefore the conclusion was considered weaker and biased. Similarly a recently published meta-analysis[43] failed to demonstrate the oncological safety and advantages of LTME over OTME. This review article presents a comprehensive assessment on the oncological safety of the LTME in addition to the proven clinical advantages of laparoscopy in the curative resections of rectal cancer. Proven clinical advantages of LTME have also been reported in in many published studies[32,33,35,42] which include the lesser blood loss, shorter length of hospital stay and lower postoperative pain score. In addition, the oncological adequacy of LTME has been confirmed in many recent publications[34,37,38,40].

Authors are fully aware of the fact that there are several limitations to this study. There is significant heterogeneity among included studies. Causes of heterogeneity are both clinical as well as methodological in terms of trial recruitment process. Included studies recruited patients with different stages of the rectal cancer and therefore one would expect their oncological outcome different. Combined analysis of studies on rectal cancer patients with and without neoadjuvant treatment can potentially influence the oncological outcomes which would result in biased conclusions. Variable grade and stage of the disease in recruited patients can also manipulate overall

survival and risk of recurrence. Preoperative nodal disease staging by MRI scan is a standard approach and all included studies did report the use of this imaging prior to surgery. Preoperative diagnostic and staging modalities across the included trials were significantly heterogeneous and therefore can potentially be a strong source of study sample contamination leading to biased outcomes. Colorectal follow up protocol among various centres conducting these trials was significantly diverse and inconsistent. Future trials should be directed towards the involvement of major colorectal units recruiting patients of similar stage and grade of the disease with different arms evaluating outcomes with and without neoadjuvant chemoradiotherapy. In addition, an agreed preoperative staging as well follow up protocol will also help to curtail the clinical and methodological flaws reported in previous trials.

COMMENTS

Background

Total mesorectal excision (TME) has been the gold standard treatment for the management of rectal cancer. Laparoscopic approach for TME has been reported with several advantages such as quicker recovery, reduced postoperative pain and shorter hospital stay. But the limitations compared to open approach include higher cost, longer learning curve and longer operating time.

Research frontiers

Due to clinically measureable advantages, the laparoscopic approach may be a preferred way forward as long as oncological safety of both approaches is at least similar. Several non-randomized and randomized studies have reported the inconsistent oncological findings following laparoscopic TME and precise guidelines are still scarce. Since the introduction of new generation of laparoscopic instruments and stapling devices, the recently published studies have reported encouraging results in favour of laparoscopic TME.

Innovations and breakthroughs

This article highlights the role of laparoscopic approach for TME in current situations. This article reports the oncological safety of laparoscopic TME in terms of clear circumferential resection margins, number of harvested lymph nodes, recurrence and mortality following both open and laparoscopic TME. This article compared to other peer review publications on the same subject provides the latest and strongest evidence and may assist the colorectal surgeons in decision making.

Peer review

It is an important topic, clear presentation, good readability, appropriate methods, precise results, interesting discussion, coherent tables, unambiguous conclusion. This is a very good paper.

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EDITORIAL

Performing colonoscopy in elderly and very elderly patients: Risks, costs and benefits

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Abstract

Many diagnostic and screening colonoscopies are performed on very elderly patients. Although colonoscopic yield increases with age, the potential benefits in such patients decrease because of shorter life expectancy and more frequent comorbidities. Colonoscopy in very elderly patients carries a greater risk of complications and morbidity than in younger patients, and is associated with lower completion rates and higher likelihood of poor bowel preparation. Thus, screening colonoscopy in very elderly patients should be performed only after careful consideration of potential benefits, risks and patient preferences. On the other hand, diagnostic and therapeutic colonoscopy are more likely to benefit even very elderly patients, and in most cases should be performed if indicated.

Key words: Colonoscopy; Elderly; Colon polyp; Colon cancer; Screening; Surveillance; Complications; Yield; Bowel preparation

Core tip: Although colonoscopic yield increases with age, the potential benefits in elderly patients decrease because of shorter life expectancy and more frequent comorbidities. Colonoscopy in very elderly patients carries a greater risk of complications and morbidity than in younger patients. Thus, colonoscopy in elderly patients should be performed only after careful consideration of potential benefits, risks and patient preferences.

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INTRODUCTION

Colonoscopy is currently the procedure of choice for whole colon evaluation in patients who present with lower gastrointestinal symptoms. In the United States, it is also the most effective and most commonly used modality for colorectal cancer (CRC) screening in asymptomatic individuals (with or without a family history), and for surveillance in patients with a personal history of adenomatous polyps, CRC or inflammatory bowel disease. Finally, in appropriate circumstances it is an important therapeutic procedure, allowing for biopsy of suspicious lesions, treatment of bleeding sources, placement of stents, and, most of all, removal of colorectal adenomatous polyps, thereby preventing the potential occurrence of CRC[1].

COLONOSCOPY IN ELDERLY PATIENTS

Because the incidence of colorectal pathology and symptoms increase with age, a large proportion of diagnostic, screening and surveillance colonoscopies are performed on "elderly" (defined as those > 65 years of age) and "very elderly" patients (> 80 years). In North America, the number of screening procedures in elderly patients has increased dramatically ever since many in-

surance programs, including medicare, began to cover screening colonoscopy in average-risk beneficiaries[2,3]. However, performing colonoscopy in elderly patients poses a unique set of challenges. In the elderly, the risks and benefits of colonoscopy should be carefully assessed in light of lower life expectancy and the frequent presence of co-morbidities, so as to ensure that the potential benefits outweigh the risks and morbidity. This review will discuss issues pertaining to the procedural yield, potential benefits, technical feasibility, complication risks, logistical difficulties and costs associated with performing colonoscopy in elderly and very elderly individuals.

YIELD

The procedural yield is the percentage of patients who are found to have clinically significant findings (especially neoplasia) on colonoscopy. Generally, the yield of colonoscopy increases with age[4]. According to Surveillance Epidemiology End Results (SEER) registry data as of 2007, the incidence of CRC is 120 cases per 100000 in persons aged 50-64 years of age, 186 per 100000 in those 65-74, and 290.1 per 100000 in those ≥ 75[5]. It is well established that elderly patients have a higher prevalence of colorectal neoplasia[6,7], as well as other findings such as diverticulosis and hemorrhoids. As with younger patients, symptomatic elderly patients demonstrate a higher yield than those who are asymptomatic[8].

Numerous studies have confirmed high yields for both screening and diagnostic colonoscopy in elderly patients (Table 1). The reported yield of CRC in symptomatic elderly patients has ranged from 3.7% to 14.2%[9-12]. In a study on 200 symptomatic octogenarians, 80% had colonoscopic findings that explained their symptoms[13]. Controlled studies that compared the yield in patients of different ages have echoed these findings. In one study on 1353 elderly patients, the risk of CRC development was higher in patients > 80 compared to those 70-74 years old[6]. In another study that included 915 symptomatic and screening patients, more advanced adenomas and invasive cancers were identified in 53 patients over the age of 80 than in younger controls[14]. Studies on European patients as well as minority groups in the United States have also reported similar results. A large study on 2000 English patients showed that compared with younger patients, those > 65 years old had higher overall diagnostic yields (65% *vs* 45%) as well as CRC prevalence (7.1% *vs* 1.3%)[15], while another study on 1530 African American and Hispanic patients showed that the CRC yield was significantly higher in those over 65 years of age than in younger counterparts (7.8% *vs* 1.8%)[16].

COMPLICATIONS AND ADVERSE EVENTS

One of the main concerns with performing colonoscopy on elderly patients is the potential for increased risk of complications. Adverse events are typically categorized as those occurring during or immediately after the procedure and those with a delayed presentation. Cardiopulmonary complications are the most common peri-procedural adverse events. The level of sedation, presence of comorbidities and procedure length and complexity all contribute to the risk and should be addressed to the extent known during pre-procedural planning, especially for elective colonoscopies.

Although early, small studies suggested that colonoscopy in elderly patients did not result in more complications[17], more recent, larger and better designed studies have shown convincingly that colonoscopy in the elderly is associated with more risk than in younger patients. As demonstrated by a recent meta-analysis, very elderly patients had a significantly higher rate of overall adverse events, including gastrointestinal bleeding and perforation[18] (Table 2). Studies from Asia have also reported higher risks of cardiovascular complications despite the fact that elderly patients on average received lower doses of sedatives[19].

Nevertheless, when taken in context, the complication rate is still quite low even for patients over 85 years of age, and in most cases colonoscopy can be done safely with appropriate monitoring and precautions[20]. Furthermore, several studies have shown that propofol sedation, despite its propensity to lower blood pressure, can be used safely in elderly patients[21-23]. The overall major

Table 1 Yield of colonoscopy in studies with subgroups of symptomatic and/or screening/surveillance "elderly" patients

Ref.	*n*	Age (yr)	Completion	Cancers	Adenomas/ polyps
Bat *et al*[10], 1992	436	80+	63%	14%	29.80%
Ure *et al*[48], 1995	354	70+	78%	6%	24%
Sardinha *et al*[49], 1999	403	80+	94%	4.50%	-
Clarke *et al*[12], 2001	95	85+	-	12.70%	-
Lagares-Garcia *et al*[50], 2001	103	80+	92.70%	11.60%	19.40%
Arora *et al*[51], 2004	110	80+	97%[1]	20%	-
Syn *et al*[9], 2005	225	80+	56%	11%	25%
Yoong *et al*[52], 2005	316	85+	69%	8.90%	14.20%
Karajeh *et al*[15], 2006	1000	65+	81.80%	7.10%	6%[2]

[1]Adjusted for non-traversable stricture; [2]Large polyps ≥ 1 cm in size.

Table 2 Complication risks based on data from meta-analysis by Day *et al*[18]

Age group (yr)	> 65	> 80
Cumulative adverse events	26.0[1] (25.0-27.0)	34.9[1] (31.9-38.0)
Perforation	1.0% (0.9-1.5)	1.5% (1.1-1.9)
Gastrointestinal bleeding	6.3% (18.0-20.3)	2.4% (1.1-4.6)
Cardiopulmonary complication	19.1% (18.0-20.3)	28.9% (26.2-31.8)
Mortality	1.0% (0.7-2.2)	0.5% (0.006-1.9)

[1]Per 1000 colonoscopies.

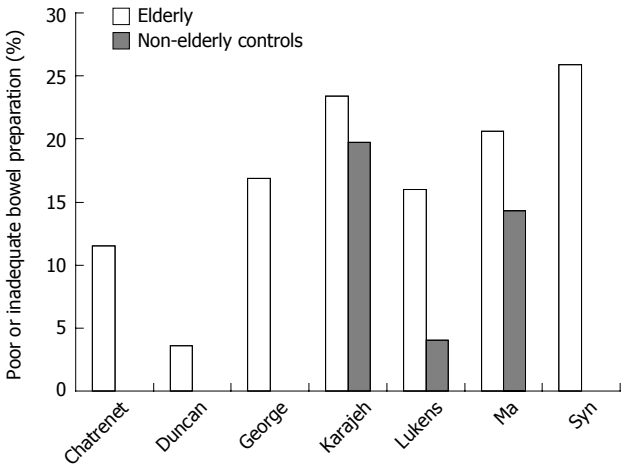

Figure 1 Published studies reporting rates of poor or inadequate bowel preparation for colonoscopy in elderly patients and non-elderly controls: Chatrenet[13], Duncan[11], George[53], Karajeh[15], Lukens[31], Ma[19] and Syn[9].

complication rate in patients over 80 is low, between 0.2% and 0.6%[11,15], although it increased with specific comorbid conditions[24]. A large retrospective study reported an overall perforation rate of 0.082% for adults undergoing colonoscopy, with advanced age as a significant predictor[25]. Studies in minority patients in the United States (African Americans and Hispanics)[16], as well as from Asia[26], have also reported that complication rates are low in elderly patients. When determining procedural risk, physiological age, *i.e.*, presence of comorbidities, is more important than chronological age. Thus, the overall health status of the patient should be considered, instead of relying on rigid age cutoffs.

During colonoscopy, the vital signs, oxygen saturation and cardiac rhythm of all patients should be monitored continuously. Supplemental oxygen is often administered if patients are sedated. Increasingly, capnography is being used to identify early signs of respiratory depression. Conscious sedation is achieved by the use of a short-acting sedative with amnestic properties, such as intravenous midazolam or diazepam, and an opioid analgesic, such as fentanyl or meperidine. The use of deep sedation with propofol, typically administered by an anesthesia provider, is becoming more popular in the United States. However, gastroenterologist-administered propofol has also been shown to be safe in the elderly[22].

Up to one third of patients may have minor side-effects after outpatient colonoscopy, most frequently bloating or abdominal cramps. Depending on their level of independence, elderly patients living alone may require additional post-procedure care. Post-procedure calls within 48 h by medical staff may be helpful.

Many elderly patients have implanted cardiac pacemakers or defibrillators. The use of monopolar electrocautery during snare polypectomy can cause pacemaker inhibition or false detection of cardiac arrhythmias[27]. Thus, these devices are generally inactivated during the colonoscopy.

COLONOSCOPY COMPLETION RATES

Complete colonoscopy requires cecal intubation or, for those who have had an ileocecectomy, reaching the ileocolonic anastomosis. In the United States, studies on patients of all ages undergoing elective screening or surveillance colonoscopy report high completion rates above 95%[28]. Studies on symptomatic patients (including those with non-traversable obstructing lesions) report completion rates of around 83%[29].

Colonoscopy in the elderly is technically more challenging than in younger patients because of various factors, including more extensive diverticulosis, higher incidence of tortuosity or post-surgical adhesions, and higher risk of complications[4]. Elderly patients are also less likely to tolerate large amounts of sedation, and have a higher probability of suffering inadequate bowel preparation[13,30,31], both of which can preclude complete colonoscopy.

A wide range of completion rates in elderly patients have been reported, including 56% (this included 8 obstructing lesions that could not be traversed)[9], 63% (on the first attempt) or 89% (second attempt)[10], 83.5%[13], and as high as 88.1% (for patients > 73 years old)[30]. For patients in their late 60's, the completion rate was quite respectable at 90.3% in one study[16], while a prospective study reported an "endoscopic success rate" of 90% for octogenarians[31]. Overall, a meta-analysis showed that for elderly patients > 65 years of age, the mean completion rate was 84%, while for those > 80, the completion rate was 84.7%[18]. Many of the studies that directly compared completion rates between elderly patients and younger controls showed a significant difference in favor of the younger group[16,31,32].

BOWEL PREPARATION ISSUES

In a previous meta-analysis of 20 studies, suboptimal bowel preparation was documented in 18.8% of patients > 65 years of age, and in 12.1% of those > 80[18]. As summarized in Figure 1, elderly patients have a higher likelihood of poor bowel preparation due to slower colonic transit and higher incidence of obstipation[4,33]. Inadequate bowel preparation was a big factor in many studies that demonstrated lower colonoscopy completion rates in older patients[13,30,31]. The most commonly used bowel preparation regimen, 4 L of pegylated ethylene glycol, represents a substantial ingestion volume for elderly patients, who are also more likely to have renal, cardiac or hepatic conditions that make them ineligible for small volume alternative osmotic laxatives, such as sodium sulfate or sodium picosulfate. Moreover, frequent trips to the commode constitute a fall risk for the frail elderly patient with mobility issues.

DECISION ANALYSES

Several decision analysis studies have addressed the costs,

Table 3 Outcomes for 1244 individuals who underwent screening colonoscopy; classification is according to the most advanced lesion for each patient[41]

Age group (yr)	*n*	Patients with advanced neoplasia	Mean life-expectancy (yr)	Mean polyp lag time[2] (yr)	Mean LE extension (yr)	Adjusted mean LE extension
50-54	1034	33[1] (3.2%)	28.87	5.23	0.85	2.94%
75-79	147	7 (4.7%)	10.37	5.44	0.17	1.64%
80+	63	9[3] (14%)	7.59	3.58	0.13	1.71%

LE $_{extension}$: Extension of life expectancy due to screening colonoscopy. Adjusted LE $_{extension}$ (%) = (LE $_{extension}$/LE) × 100. [1]Includes one patient with high grade dysplasia and two patients with cancers; [2]These values are calculated only for patients with neoplastic findings, not the entire group; [3]Includes two patients with high-grade dysplastic polyps and one with cancer.

risks and benefits of colonoscopy in elderly patients. The potential for screening-related complications was greater than the estimated benefit in some population subgroups aged 70 years and older. At all ages and life expectancies, the potential reduction in mortality from screening outweighed the risk of colonoscopy-related death[34]. In another study, a patient with no familial risk factors with negative colonoscopy at age 50, 60 or 70 is less likely to benefit from additional screening colonoscopy compared to a 75 years old individual with no antecedent screening. Furthermore, an individual in superb health at age 80 may benefit from colonoscopy whereas a patient with prior low risk adenomas but moderate to severe health impairment is unlikely to benefit from colonoscopy even at age < 75. Upfront investment in screening and polypectomy in younger persons may decrease ultimate CRC-related costs, including subsequent screening and surveillance, for older Americans. While these savings could potentially be offset by future health costs for other diseases in the elderly, screening 50 years old persons would still be cost-effective[35].

EQUIPMENT AND LOGISTICAL ISSUES

Colonoscopes and accessories are the same for elderly patients as their younger counterparts, although some endoscopists favor pediatric colonoscopes because the more flexible shaft can facilitate passage in the presence of tortuosity or diverticulosis. All patients undergoing sedation need an adult escort after the procedure, potentially posing a burden on some elderly individuals living in social isolation.

OVERVIEW: SCREENING COLONOSCOPY IN ELDERLY PATIENTS

In the absence of additional risk factors such as family history, the prevailing consensus is to begin screening at age 50 and to continue at intervals determined by the screening modality used, as well as any history of adenomatous polyps or cancer. Currently, all three major United States gastroenterology societies (American Gastroenterological Association, American Society of Gastrointestinal Endoscopy, and American College of Gastroenterology), the American Cancer Society and the United States Preventive Services Task Force (USPSTF) have endorsed screening colonoscopy beginning at age 50 for average risk patients, with subsequent intervals of every 10 years in the absence of any personal history of adenomas or family history of CRC[36-39]. However, the USPSTF is the only body to recommend discontinuation of screening in average-risk individuals at age 75[39]. In a publication on colonoscopy developed by the American Gastroenterological Association for the American College of Physicians "Choosing Wisely" Campaign to control health care costs, it is stated that "routine (colonoscopies) usually aren't needed after age 75."

There is concern that continued screening in very elderly individuals is associated with diminishing utility and increasing costs, morbidity and risks to both individual and society. Life expectancy in light of advanced age and co-morbidities should be considered when considering screening in very elderly persons. Screening may not be warranted in asymptomatic patients for whom detecting and removing precancerous polyps would be unlikely to change their long term survival. Moreover, elderly patients who have been screened often incur frequent early repeat colonoscopies, leading to additional risk, morbidity and cost[40].

In a previous study using Declining Exponential Approximation of Life Expectancy analysis, we found that the prevalence of neoplasia was 13.8% in 50-54 years old patients, 26.5% in the 75 to 79 years old group, and 28.6% in the group aged 80 years or older. Despite higher prevalence of neoplasia in elderly patients, estimated mean extension in life expectancy was much lower in the group aged 80 years or older than in the 50 to 54 years old group (0.13 years *vs* 0.85 years). Even though prevalence of neoplasia increases with age, screening colonoscopy in very elderly persons (aged ≥ 80 years) results in only 15% of the expected gain in life expectancy in younger patients (Table 3)[41]. In a similar study, the survival of elderly patients undergoing colonoscopy was significantly lower than that for younger patients, with important screening implications[42]. Another decision analysis also showed that the benefits of screening were outweighed by screening-related complication risks in subgroups of patients over 75, especially if they were in poor health[34]. Surveys have shown that providers do incorporate age and comorbidity in screening recommendations; however, their recommendations were often inconsistent with guidelines[43]. Other factors come into

play when screening decisions are made; for example, elderly patients of low socioeconomic class were less likely to be screened for CRC regardless of insurance status[44].

OVERVIEW: DIAGNOSTIC COLONOSCOPY IN ELDERLY PATIENTS

Many gastrointestinal conditions, such as constipation, incontinence, diverticulosis and hemorrhoids, are more common with advancing age. CRC is much more common in symptomatic patients over 65 than in younger controls, with a risk ratio as high as 17[45]. In all patients with colorectal symptoms, colonoscopy is usually the preferred diagnostic test for whole colon evaluation and has supplanted barium enemas and sigmoidoscopy. Direct visualization of the colonic mucosa can be extremely useful for the diagnosis of colitis and confirmation of polyps or masses. Of course, colonoscopy also allows for histologic assessment through biopsies. Certainly any elderly patient without prior colonoscopy who presents with significant new colorectal symptoms should be offered diagnostic colonoscopy.

One of the most common colorectal symptoms leading to hospitalization is lower gastrointestinal bleeding. With advancing age there is an increased incidence of bleeding from diverticulosis, arteriovenous malformations, malignancy, ischemic colitis, radiation colitis and ano-rectal lesions. When feasible, colonoscopy is the best diagnostic test and may offer therapeutic options. In elderly hospitalized patients, completing a 4 L polyethylene glycol preparation can be difficult; sometimes placement of a nasogastric tube is required. As an alternative diagnostic modality, the technetium red blood cell scan can localize active bleeding, while angiography is another diagnostic option, and like colonoscopy offers therapeutic possibilities.

OVERVIEW: THERAPEUTIC COLONOSCOPY IN ELDERLY PATIENTS

Colonoscopy offers a variety of therapeutic options to control bleeding, remove polyps and small tumors, and relieve colonic obstruction due to benign or malignant strictures; these maneuvers are especially useful in elderly patients because they may obviate the need for surgery. However, small polyps may not need to be removed because the relative complication risk is high and the benefit is probably low[41].

For bleeding patients, endoscopic hemostasis can be achieved using epinephrine injection, thermal or electrocoagulation, or deployment of clips. Polypectomy is performed in the same manner independent of age, *i.e.*, small polyps are removed with cold snare polypectomy or biopsy forceps, larger polyps are removed with snare polypectomy with monopolar coagulation, and flat or sessile polyps are removed after saline submucosal injection, perhaps supplemented by argon plasma coagulation. With increasing age, large and flat polyps are more common. Benign colonic strictures may be seen in patients with a surgical anastomosis, or in the presence of chronic ischemic colitis, inflammatory bowel disease or diverticulitis. In such patients, endoscopic dilation can be attempted under fluoroscopic observation. Malignant strictures are at greater risk of perforation with dilation. In selected patients with colonic malignancy who are not surgical candidates or who need preoperative decompression, self-expanding stents can be placed across the obstruction. Studies on endoscopic mucosal resection and endoscopic submucosal dissection have included small numbers of elderly and very elderly patients, showing that these procedures are possible even in advanced age, although there are significant complication risks similar to those seen in younger patients[46,47].

CONCLUSION

Colonoscopy in very elderly patients (over 80 years of age) carries a greater risk of complications, adverse events and morbidity than in younger patients, and is associated with lower completion rates and higher chance of poor bowel preparation. Although colonoscopic yield increases with age, several studies have suggested that the potential benefits are significantly decreased because of shorter life expectancy and greater prevalence of comorbidities. Thus, screening colonoscopy in very elderly patients should be performed only after careful consideration of potential benefits, risks and patient preferences. Diagnostic and therapeutic colonoscopy are more likely to benefit even very elderly patients, and in most cases should be performed if indicated.

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REVIEW

Colonoscopy, pain and fears: Is it an indissoluble trinomial?

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Abstract

Colonoscopy is the reference method in the secondary prevention, diagnosis and, in some cases, treatment of colorectal cancer. It can often cause pain associated with embarrassment, anxiety, and physical and emotional discomfort. Pain intensity is influenced by a lot of factors, and there is a strict relationship among pain, pain perception, and mind. Several methods can be used to break the trinomial colonoscopy, pain and fear. Sedoanalgesia is recommended by several guidelines. If no sedation is offered, the patient must accept a higher chance of unacceptable discomfort and the endoscopist a lower chance of completing the procedure because of patient discomfort. Other non-pharmacologic methods such as acupuncture, music, and hydrocolonoscopy can be used as alternatives to pharmacologic sedoanalgesia. Furthermore, new endoscopic technologies such as variable-stiffness colonoscopes and ultrathin colonoscopes, or the use of carbon dioxide instead of air for colon insufflation, can reduce the pain caused by colonoscopy. In the future, technical improvements such as wireless capsules or robotic probes, will probably enable to overcome the present concept of colonoscopy, avoiding the use of traditional endoscopes. However, at present the poor attention paid by endoscopists to the pain and discomfort caused by colonoscopy can not be justified. There are several methods to reduce pain and anxiety and to break the trinomial colonoscopy, pain and fear. We must use them.

Key words: Colonoscopy; Pain; Fear; Anxiety; Discomfort; Conscious sedation

Core tip: Colonoscopy can often cause pain associated with embarrassment, anxiety, and physical and emotional discomfort. Control of discomfort and pain during colonoscopy is considered to be a high priority by patients. This review of the literature encompasses the main methods for reducing pain and anxiety, to break the trinomial colonoscopy, pain and fear.

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INTRODUCTION

At present, colonoscopy is the reference method in the secondary prevention, diagnosis and, in some cases, treatment of colorectal cancer[1,2]. For this reason, and as a consequence of the improvement of both imaging techniques (for instance, magnification) and interventional procedures (ESD), and the screening programs for the colon cancer prevention that are ongoing in many countries, the annual number of colonoscopies is strongly increasing. However, colonoscopy is considered highly invasive and is usually assumed to be an uncomfortable and often painful procedure. These concerns can result in anxiety that unfavourably decreases patient cooperation and satisfaction with the procedure[3]. Therefore, analgesia and sedation are frequently used. The decision to use premedication and the kind of premedication are influenced by national and cultural differences among

countries[4,5]. Moreover, there is a wide variation in colonoscopy practice also among centers in the same country[6], probably caused by the poor attention paid to the pain control during invasive procedures[7].

However, the fear of experiencing pain during colonoscopy can cause the patient refusal to undergo the examination, with possible negative implications on both diagnosis and treatment. Several studies showed that fear of being embarrassed or fear of pain during colonoscopy were positively associated with unwillingness to participate in colorectal cancer screening[8,9].

Therefore, it is quite evident that colonoscopy, pain and fear (of being embarrassed during colonoscopy, of experiencing pain, of having cancer, *etc.*) are strictly linked together, and only reducing the procedure-related patient discomfort can break such a trinomial, making colonoscopy more accepted with increase of the diagnostic yield.

In this review, we will discuss the relationship among fear, anxiety, and pain, as well as the ways of breaking the trinomial colonoscopy, pain, and fear.

RELATIONSHIP AMONG PAIN, FEAR, AND ANXIETY

All invasive procedures can cause pain associated with embarrassment, anxiety, and fear. Such a situation was defined by Morrison as "discomfort"[10]. Discomfort can be physical (malaise and trouble due to the duration of the procedure, need to maintain an uncomfortable position, or need to remain motionless for a long time); or emotional (embarrassment of showing the body, anxiety and fear of experiencing pain, anxiety and fear of an unfavorable diagnosis). Pain intensity during an invasive procedure varies according to patient compliance, and is influenced by a lot of factors, such as previous experience, pre-existing pain and/or chronic pain, presence of fear or anxiety, type and duration of the procedure, and related expectation of pain[10,11]. There is a strict relationship among pain, pain perception, and mind, and mind-body medicine can examine interactions as they occur among the brain, mind, body, and behavior[12]. Mind can be defined as "conscious and unconscious thought patterns, including images, perceptions and intentions, generated by a functional network of distributed neural centers in the brain and body, including homeostatic representations that provide the context for human self awareness and emotional experience"[12]. An expanding evidence base reveals that the limbic system (in particular the amygdala) has the capacity to up- or down-regulate pain's emotional response[13].

Fear represents a normal emotional response to a threat that is true, or is recognized as true by the individual (*i.e.*, fear of colonoscopy and related pain). Conversely, anxiety is an irrational state of mind, characterized by a sensation of uncertainty and inadequacy and often associated with neurovegetative symptoms (such as tachycardia, hypertension, tachypnea, shakes, and so on), and can become a pathological and distressing condition[14].

Pain can cause both immediate and long-term harmful effects. The effects of acute procedural pain consist of a variety of physical, emotional, behavioral, cognitive, and psychological manifestations, including fear, anxiety, anger, aggressive behavior, inability to concentrate, embarrassment, refusal to consent to further procedures, and distrust of the health care team, and may effect overall economic, social, and spiritual well-being[15-17]. For these reasons, a recent position statement on the procedural pain management recommends the use of anxiolytic drugs associated with analgesics to manage the pain related to medical procedures. Furthermore, methods of non-pharmacologic management are also recommended during all phases of the procedures[18].

Patient experience is a critical aspect of medical procedures, in particular of endoscopic procedures. Patients with favorable endoscopy experience are more likely to comply with medical advice, adhere to screening and use medical service in the future, whereas patients with poor experience are more likely to leave their care provider and be less compliant[19].

A systematic review of literature showed that the control of discomfort and pain during the colonoscopy was considered to be a high priority by patients[20].

Given the mind's ability to influence the pain perceived during colonoscopy, acting on the pain and/or patient's discomfort is mandatory to break the trinomial "colonoscopy, pain and fears".

SEDOANALGESIA AND OTHER METHODS TO REDUCE PAIN

Sedoanalgesia practices

The use of sedoanalgesia by administering *iv* drugs for lower gastrointestinal endoscopic procedures is strongly recommended by several guidelines. If no sedation is offered, the patient must accept a higher chance of unacceptable discomfort and the endoscopist a lower chance of completing the procedure because of patient discomfort[21]. However, the use of sedation for lower gastrointestinal endoscopic procedures is considerably influenced by the cultural differences among countries and the rules which regulate the drugs use[4,5].

Propofol deep sedation is frequently used in some countries, whereas in other ones conscious sedation induced by means of a combination of a benzodiazepine and an opioid is more frequently used[22-24]. Recently, a new option for sedation has been approved by the Food and Drug Administration. It is a Computer Assisted Personalized Sedation system called the SEDASYS® System (Ethicon Endo-Surgery, Inc., Cincinnati, OH, United States), that is indicated for the intravenous administration of Propofol for the initiation and maintenance of minimal to moderate sedation for ASA I or II patients undergoing endoscopic examination. Although the intention of this approval is to cut the anesthesia related

expenses, at present this system is scarcely used. Consequently, in many countries-such as Italy-moderate sedation using benzodiazepine (like Midazolam) and an opioid (like Pethidine), is the most popular method of sedation, although the use of Propofol is progressively increasing, because the satisfaction of both patients and endoscopists is greater. Moreover, recovery and discharge times are shorter with the use of Propofol[25,26].

Several other drugs can be used for colonoscopy sedation, such as Alfentanyl, Fospropofol, Remifentanil, Remimazolam[5]. However, some of these drugs are still scarcely used, because they have been marketed quite recently, and can be only used by anaesthetists.

The optimal sedative for colonoscopy should be short acting, safe, easy to administer, and with minimal side effects, but this sedative is yet to be found. In this perspective, the use of nitrous oxide gas as an alternative method to *iv* sedoanalgesia for colonoscopy appears quite interesting and promising. Two systematic reviews suggest that nitrous oxide gas provides comparable analgesia with the advantage of a shorter recovery time and greater safety than *iv* analgesia-sedation methods used during colonoscopy[27,28].

However, all sedoanalgesia methods can cause adverse cardio-respiratory events, even though the incidence of serious adverse events is low with all currently available agents[29]. Some other methods that do not require the *iv* administration or the inhalation of drugs are reported in the literature to reduce patient's discomfort and to increase the acceptability of the examination.

Acupuncture

The use of this ancient technique displayed several effects on gastrointestinal tract, and a United States National Institute of Health consensus statement published in 1998 indicated that acupuncture might be useful for the treatment of certain pain conditions[30].

In 2003, Fanti *et al*[31] conducted a randomized placebo-controlled study to evaluate the analgesic effect of electro-acupuncture in a group of patients who were undergoing colonoscopy. They found that patients in the acupuncture group reported not significantly reduced pain during the procedure. Some years later, Ni *et al*[32] reported a randomized study on two groups of 40 patients undergoing colonoscopy. In the first group, acupuncture was performed in the traditional points ST 36, ST 37, SP 9, SP 6, LI 4 from 30 min before colonoscopy to the end of the procedure; in the latter group no treatment was performed. Cecum was reached significantly more frequently, and discomfort resulted less marked, in the patients who underwent acupuncture. The same authors reported similar results in a subsequent study, in which they also observed lower plasma concentrations of beta-endorphin in the patients treated with electro-acupuncture, confirming a meaning attenuation of the patients' stress response during colonoscopy after electro-acupuncture[33].

However, on the basis of these data and some few other studies with conflicting results, currently available data do not support the use of acupuncture as an analgesic adjuvant during colonoscopy[34].

Audio distraction

Listening relaxing music during pain-invoking experience is considered to have a therapeutic effect, as it promotes relaxing responses, triggers positive associations, and diverts attention from anxiety[35]. For this reason, music has been used to decrease anxiety levels in patients in a variety of scenarios, such as digestive and bronchial endoscopy[36,37]. However, the studies published in the literature are very heterogeneous as concerns either the type and design of the study, or the type of music used (classical, easy-listening, relaxing, Turkish classical music, *etc*.). Moreover, also the results are often conflicting.

From 2007 to 2009 three meta-analyses were published on this topic. The first of them included six randomized controlled trials that involved 641 patients undergoing esophagogastroduodenoscopy, flexible sigmoidoscopy or colonoscopy, with or without intervention through music therapy. This meta-analysis yielded significantly lower anxiety levels, reduction in analgesia requirements, reduction in sedation requirements, and procedure times in patients receiving music therapy in comparison with controls[38].

The second meta-analysis dealt with the effect of music on procedure time and sedation during colonoscopy. Eight randomized controlled trials for a total of 722 patients enrolled were included into the meta-analysis, that concluded that music is effective in reducing procedure time and sedative requirement during endoscopic examination[39].

Also the third meta-analysis dealt with the effect of music during colonoscopy[40]. One hundred and seven articles were examined, but just 8 randomized controlled trials for a total of 712 patients enrolled met the inclusion criteria. Music played during colonoscopy was shown to improve patients' overall experience, but it did not alter other parameters, such as sedative pain medication requirements, procedure times, patients' pain, and patients' willingness to repeat the same procedure in the future.

Finally, Lee *et al*[41] designed a prospective randomized controlled trial to test the hypotheses that visual distractions could reduce the requirement for sedatives during colonoscopy, and that the combination of audio and visual distractions could have additive beneficial effects. One hundred and sixty-five patients were randomly allocated into three groups to receive different modes of sedation: visual distraction plus sedation, audio-visual distraction plus sedation, sedation alone. Visual distraction alone did not decrease the dose of sedative medication required for colonoscopy. When audio distraction was added, both the dose of sedative medication required and the pain score decreased significantly.

Hydro-colonoscopy and other substances instilled into the colon

Historically, air insufflation was used to advance the

colonoscope through the colon. In 1984, Falchuk and Griffin[42] described a water technique that facilitated colonoscopy in patients with severe diverticular disease. Fifteen years later, a prospective randomized study on 100 unsedated patients undergoing colonoscopy showed that the passage through the left colon was significantly faster with the water intubation method than with the traditional method[43]. Afterwards, several studies investigated the usefulness of this technique, based on the assumption that the instillation of water at 37 ℃ into the colic lumen could minimize colon spasms, reducing pain and maintaining the same efficacy of air in reaching the cecum. The water weight would enable to enlarge the lumen without stretching the colon walls. However, this technique requires a thorough colon cleansing to allow a good visualization of the lumen.

In 2012, a systematic review and meta-analysis of randomized controlled trials on hydro-colonoscopy examined nine studies for a total of 1283 patients enrolled. Warm water infusion resulted less painful than standard air insufflation, reducing the need for sedation/analgesia, and improving patient acceptance of colonoscopy[44].

Some authors proposed also the corn seed oil assistance in colonoscopy. Theoretically, warm water is thought to decrease spasm of the colon and straighten the sigmoid colon due to the gravity of water when the patient is in the left decubitus. On the other hand, oil lubrication decreases the friction between the colonic mucosa and the shaft of the scope, but it is devoid of the aforementioned effects by warm water. Brocchi *et al*[45] performed two prospective, randomized and controlled studies comparing the oil method with a standard technique in one[46] and with a warm water technique in the other. The results of the two studies were similar and consistent with a favorable effect of the oil technique on successful intubation to the cecum, level of patient pain, and degree of difficulty during colonoscopy.

Beside warm water and corn seed oil, other substances have been instilled into the colon to reduce spasms. Peppermint oil has a satisfactory spasmolytic effect on the smooth musculature of colon. Asao *et al*[47] instilled a solution of peppermint oil through the accessory channel of the colonscope in 409 patients undergoing colonoscopy. About twenty seconds later, they documented a relaxation of the musculature that lasted about twenty minutes. Finally, Ai *et al*[48] evaluated the antispasmodic effect of the Chinese herbal medicine Shakuyaku-kanzoto (TJ-68) on the colonic wall by direct spraying during colonoscopy. TJ-68 is an extract powder composed of Shakuyaku (*Paeoniae radix*) and Kanzo (*Glycyrrhizae radix*) combined at a ratio of 1:1, and inhibits acetylcholine-induced contraction and the contractile machinery of the smooth muscle.

The authors conducted a randomized study on 101 patients, and concluded that direct spraying of TJ-68 on the colonic mucosa suppressed colonic spasm. However, the effectiveness use of TJ-68 has been evaluated in just few studies, and there are no systematic reviews and meta-analyses supporting its actual clinical usefulness.

NEW ENDOSCOPIC TECHNOLOGIES FOR COLON EXAMINATION

Fixed, angulated sigmoid colons or long, floppy colons are the main causes of both the difficulty of reaching the cecum and the pain experienced by the patient. Several studies have been designed to evaluate the use of pediatric colonoscope for colonoscopy in adults, based on the assumption that the pediatric colonoscope could provide greater comfort in adult patients, because of its smaller diameter and greater flexibility. The results of these studies showed that the pediatric colonoscope is suitable for colonoscopy in adult, and is also useful in patients in whom colonoscopy with the adult colonoscope is unsuccessful in reaching the cecum[49]. Furthermore, ultrathin colonoscopes (diameter 9.2 mm) are available today, and theoretically they should allow for a further reduction of the pain experienced by the patient. However, at present there is no evidence about such an assumption. Moreover, an initial "learning curve" is needed in using these colonoscopes for endoscopists used to an adult colonoscope, because the ultrathin tool is quite less stiff, and more pull-back maneuvers are required during the examination.

The need of flexibility must often be balanced with the need of stiffness, to avoid the risk of creating loops in the mobile tracts of the colon. In the last years, variable-stiffness colonoscopes have become available in both adult and pediatric classes. These new tools have a stiffness control ring that allows to modify the flexibility during the examination, reducing the risk of creating loops in the left tract of the colon, and allowing for a higher cecal intubation rate with less abdominal pain, according to the conclusion of a meta-analysis of randomized controlled trials published in 2009[50]. However, the results of the comparison between variable-stiffness colonoscope and standard adult colonoscope are conflicting. In another meta-analysis, Xie *et al*[51] concluded that variable-stiffness colonoscope significantly improved the cecal intubation, but cecal intubation time was similar for the two colonoscope types (standard and variable-stiffness colonoscopes). Moreover, the sedation dose used with the two types of instrument resulted similar; and no difference in pain scores for patients could be demonstrated, because of the differences in the scale used in the selected studies.

Insufflation of the bowel is necessary to improve visualization during colonoscopy, but it is one of the main causes of the abdominal pain experienced by the patient. It is common practice to use ambient atmospheric air, also termed "room air", to insufflate the lumen. However, the safety of carbon dioxide (CO_2) insufflation during colonoscopy is well known starting from 1974[52]. CO_2 is more rapidly absorbed from the bowel than room air, allowing for a more rapid intestinal decompression

and potentially decreasing intraprocedural and postprocedural pain. Many studies evaluated the safety and efficacy of CO_2 insufflation for gastrointestinal endoscopy. Two recent systematic reviews and meta-analysis showed that CO_2 insufflation is safe in patients without severe pulmonary disease, and is associated with decreased bowel distension and postprocedural pain[53,54]. Furthermore, one of them showed that insufflation with CO_2 in colonoscopy could also decrease abdominal pain during colonoscopy[54]. For these reasons, the use of carbon dioxide insufflation, instead of air, is currently a quality standard to maximize comfort during colonoscopy[55]. Nevertheless, the use of CO_2 for insufflation has not been widely adopted in practice for various reasons (cultural prejudices, lack of knowledge, costs, *etc*.).

In the last years, the traditional concept of colonoscopy and colon examination is changing, as new tools are going to be available. The wireless capsule colonoscopy, with the second generation of PillCam® Colon, is becoming available in routine clinical practice[56]. Likewise, the Endotics® system, that consists of a robotic probe moving forward with an inchworm locomotion, allows for the painless progression into the colon, because it does not create loops, nor cause stretching of the colon walls[57]. The applicability of the Endotics® system in clinical practice has already been proven[58], and in 2014 its second version will be marketed with an operative channel of 3 mm in diameter, that will enable to take biopsies and will open the way to perform also other operative maneuvers.

CONCLUSION

Fifty years after the introduction of flexible colonoscopy in clinical practice, psychological and religious barriers due to the indignity of the procedure, fear of the procedure related to either the procedure-related pain or possible unfavorable diagnosis, are still working to make colonoscopy, pain, and fear an apparently indissoluble trinomial.

In the future, technical improvements will probably enable to overcome the present concept of colonoscopy, avoiding the use of traditional endoscopes. However, the next availability of such technical improvements can not justify the poor attention paid by endoscopists to the pain and discomfort caused by colonoscopy, as highlighted by the variability in the use of sedoanalgesia, either among countries, or in the same country. There are several valid methods to reduce pain and anxiety and to break the trinomial colonoscopy, pain and fear. We must use them.

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Role of simulation in training the next generation of endoscopists

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Abstract

The use of simulation based training in endoscopy has been increasingly described, simulation has the potential reduce the harm caused to patients by novices performing procedures, increase efficiency by reducing the time needed to train in the clinical environment and increase the opportunity to repeatedly practice rare procedures as well as allowing the assessment of performance. Simulators can consist of mechanical devices, employ cadaveric animal tissue or use virtual reality technology. Simulators have been used to teach upper and lower gastrointestinal endoscopy as well as interventional procedures. This review reviews the currently available endoscopic simulators, and the evidence for their efficacy, demonstrating that the ability of simulators to differentiate between novice and expert endoscopists is well established. There is limited evidence for improved patient outcome as a result of simulation training. We also consider how the environment within which a simulation is placed can be manipulated to alter the learning achieved, broadening the scope of simulation to develop communication as well as technical skills. Finally the implications for future practice are considered; technology is likely improve the fidelity of simulators, increasing the potential for simulation to improve patient outcomes. The impact of the simulation environment, and the correct place of simulation within the training curriculum are both issues which need addressing.

Key words: Gastroenterology; Endoscopy; Simulation; Simulation environment; Interventional endoscopy

Core tip: Evidence is increasing that simulation is an effective means of teaching interventional procedures. We review the current use of simulators and the evidence for their efficacy, before considering the impact of the simulation environment on the learning that can be achieved. We argue that the use of the simulation environment as a tool to broaden the educational scope of simulation to teach skills other than the technical, is important to maximum utilisation of simulation.

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INTRODUCTION

Simulation has been increasingly described in endoscopy since the late 1970s. As a method of teaching it has a number of potential advantages. These include reducing the harm caused to patients by novices performing procedures[1-4], an increase in efficiency by reducing the time needed to train in the clinical environment[5], the opportunity to repeatedly practice rare procedures and assessment of performance. The use of simulation moves

the focus of an encounter firmly onto the learner, so education becomes the sole object of the exercise, which distinguishes it from clinical training, where the interests of the patient must always be placed ahead of education. In simulation, mistakes that would be unacceptable in clinical practice can be allowed to occur, providing opportunities for learning[6]. There has also been increasing interest in the use of simulation for assessment and credentialing purposes[7].

In order to further describe the use of simulation in endoscopy and its potential future role in training endoscopists, some definitions are needed. McGaghie defines simulation as: "a person, device, or set of conditions which attempts to present (education and) problems authentically. The student or trainee is required to respond to the problems as he or she would under natural circumstances[8]".

The importance of this definition is that it sees simulation as a process. A simulator, by contrast, can be seen as the device used to represent the problem itself, performing an endoscopic procedure.

The simulation environment is, importantly, distinct from the simulator. For the purposes of this review we define the simulation environment as "the context in which the simulation is placed". This definition is deliberately rather loose. The majority of the following discussion will focus on the physical space in which the simulator is placed, as well as its contents, but this environment can be seen in broader terms. How a simulation is placed within the broader curriculum of training, for example, may have a profound effect on its usefulness.

This review will discuss the various endoscopic simulators available, before considering the evidence for their efficacy. The role of the simulation environment will then be considered, before we speculate on the role of simulation in training the next generation of endoscopists.

ENDOSCOPIC SIMULATORS

Broadly, simulators currently available are able to simulate upper gastrointestinal (GI) endoscopy, lower GI endoscopy and interventional procedures. The devices available can be divided into mechanical simulators, those involving animal tissue, whether living or cadaveric and virtual reality tools.

Mechanical simulators

Mechanical simulators have been available for some time. The Erlangen plastic mannequin was described in 1974, and allowed upper GI endoscopy to be simulated[9]. These models are typically limited by a lack of fidelity (the subjective sense of how "real" a simulation is) and by a lack of variation, as the simulator is the same for every simulation.

Animal models

The use of animal tissue for endoscopic simulation has the advantage of producing a higher degree of fidelity, as animal tissue behaves more like that of a human than a mechanical model. The use of live animals in simulation has been limited by expense, the need for expensive infrastructure and ethical concerns. The use of live animals for simulating medical procedures is currently banned in the United Kingdom.

Cadaveric animal tissue has been used rather more extensively, particularly in composite simulators, where animal tissue and mechanical models are combined. This is perhaps of most use in simulators seeking to replicate interventional procedures. The Erlangen active simulator for interventional endoscopy (EASIE) (ECE-Training GmbH, Erlangen, Germany), for example, uses specially prepared cadaveric porcine organs with arteries sewn into their linings, and an electric pump to produce spurting blood[10,11]. Similar, more portable composite simulators have subsequently been developed to allow the diagnostic endoscopy, polypectomy, percutaneous endoscopic gastrostomy (PEG) gastrostomy and endoscopic retrograde cholangio-pancreatography (ERCP) to be practiced[12-14]. With the exception of anatomical variation, the placement of the porcine duodenal papilla being more proximal than the human for example, these models offer a high degree of fidelity but at the cost of the time required for preparation, requiring deep frozen animal tissue to be thawed and placed within the simulator on a baseplate[9].

Virtual reality

The introduction of virtual reality (VR) technology to simulators has had a large impact on the possibilities offered. Two commonly used examples are the GI bronch mentor (Sim-bionix, Cleveland, Ohio) and the CAE accutouch (CAE Healthcare, Montreal, Quebec, Canada; previously marketed by Immersion Medical, San Jose, California). Both simulators consist of a plastic mannequin on a trolley and possess both a mouth and an anus, allowing upper and lower GI procedures to be performed. The instruments used are standard endoscopes and the operating end and are attached to the simulator at the other. Sensors in the mannequin deliver haptic feedback to the user as well as guiding the simulation. Haptic feedback produces forces on the endoscopic which resemble those experienced in real endoscopy, thus allowing tactile as well as visual feedback to be gained by the learner. Both simulators have supplemental modules, which allow more complex procedures to be simulated. The GI bronch mentor can simulate haemostasis, flexible sigmoidsoscopy, ECRP and diagnostic EUS. The CAE accutouch has supplemental modules, which allow polypectomy, biopsy and haemostasis to be practiced.

VR simulators have a variety of potential advantages. They require very little set up time and can be used repeatedly by learners for practice. The addition of anatomical variation and varying degrees of difficulty to the simulator means that repeated procedures can be simulated with different pathologies and anatomical variations.

One of the most important features of VR simula-

tors is the ease with which performance feedback can be produced. Both the VR simulators described provide a feedback to the leaner with performance parameters including the total time of the examination, pathological findings recognised, degree of air insufflation, patient degree of discomfort, percentage of mucosa visualized and time spent in "red out" (in contact with the bowel wall)[9].

The provision of performance feedback has been recognised as an important feature of successful simulation based education[15]. The provision of feedback by the simulator itself has the potential to allow sustained practice by trainees without the need for the continuous presence of a trainer.

EVIDENCE FOR EFFICACY

Having described the simulators available, it can be seen that the potential exists to reproduce clinical scenarios outside a clinical environment. The use of simulators in training endoscopists is however, only of use if it translates into a benefit which is observable when procedures are performed on real patients, either in terms of improved performance by the trainee or, ideally, in measurable improvement in patient outcomes. The literature on simulation has, in general adopted two approaches to demonstrating the efficacy of simulators. The first is validation studies, where the end point used is performance on the simulator[16]. The two main means of validation reported are the ability of a simulator to demonstrate difference in performance between novices and experts (construct validity)[17] and the ability for practice on a simulator to produce a measurable improvement in performance[18]. The second approach is to compare the performance of simulation and non simulation trained learners in the clinical environment. As we shall see, few studies have investigated the relationship between patient outcome and simulation training.

The performance metrics produced by VR simulators make construct validity easy to demonstrate, as performance is assessed by the simulator and not by an external observer[19]. Construct validity for upper GI endoscopy was been demonstrated some time ago[20,21]. A series of studies have also demonstrated that VR simulators can distinguish novice from expert endoscopists in lower GI endoscopy (Macdonald)[22-26]. The GI mentor has also been shown to have construct validity when simulating ECRP[27]. A recent systematic review by Ansell *et al* demonstrated that the most valid metrics for training and assessment across VR simulators for colonoscopy are total procedure time, caecal intubation time, efficiency and the percentage of muscosa visualised[28]. This review also highlighted the fact that the majority of validity evidence pertains to the construct validity of VR simulators, with only one study reporting validation of a bovine model[9].

What is more difficult to demonstrate, however, is the ability of simulators to distinguish the intermediate level endoscopist from the expert[17,22,29], leading to the speculation that the role of VR simulators is limited to the teaching of basic navigational skills rather than more complex interventional procedures[5].

There is also increasing evidence from clinical studies. The overall efficacy of skills transfer into the operating room was the subject of a recent systematic review by Dawe *et al*[30], which included 10 studies looking at the effect of simulation based training on clinical performance. This concluded that the current evidence demonstrates that simulation-based training, as part of a training program and incorporating the achievement of reaching predetermined proficiency levels, results in skills that are transferable to the operative setting for laparoscopic cholecystectomy and endoscopy. Di Giulio *et al*[31] demonstrated in 2004 that simulation trained fellows performed more complete procedures and had their performance assessed as "positive" more frequently.

Looking at colonoscopy specifically, Cohen *et al*[32] randomised GI fellows to 10 h of unsupervised practice on the GI mentor or no training. Simulator trained fellows had higher competency rates during the 1st 100 cases than non-simulator trained fellows, but this effect was reduced with time. Both groups required 160 cases to achieve 90% competence. The simulation training in this study was distinguished by the absence of feedback from faculty, and by being limited to the early part of training, rather than being sustained throughout it.

The majority of the literature on training in interventional techniques has described the use of composite ex vivo simulators, which, have been shown to improve performance in several randomised trials[33-35]. These studies, however are mostly limited by the fact that assessment of skills was performed on the simulator rather than in the clinical setting, although one also demonstrated that procedure times were reduced in clinical practice in simulation trained residents and that a non significant reduction in complications occurred in their patients[35]. One randomised study has demonstrated that ERCP skills learned by novices can be shown to lead to improved performance when procedures are performed in patients[36].

In the end, one of the ultimate goals of procedural training is improved outcomes for patients. If demonstrable improvements in patient outcome can be delivered by simulation based training, then the case for its use is made. There is some evidence emerging in the laparoscopic and anaesthetic literature that the use of simulation reduces complication rates[37]. Within endoscopy, there is limited evidence. Although reduced complication rates have been hinted at in interventional procedures as described above, and one study has demonstrated improved patient comfort during conscious procedures performed by novices trained using simulation[38].

In summary, the current evidence demonstrates construct validity for VR simulation. There is evidence for improved performance in the clinical environment but this may not be maintained in later endoscopies as competence is not reached any sooner by simulation trained learners[5,39]. There is a little evidence for better patient outcome but this has only been demonstrated by one

study looking at patient comfort[38].

SIMULATION ENVIRONMENT

As we have seen, the majority of the evidence for the use of simulation to teach endoscopy and endoscopic procedures focuses on the efficacy of the use of simulators to teach practical skills. This, of course is an extremely important component of learning to perform endoscopy in the clinical environment. Adverse clinical events, which lead to the potential for harm to patients, however, are more often related to failures of communication, clinical judgement and teamwork than to technical error[40-42].

The role of simulation can be extended to allow the potential for teaching skills beyond the technical if the simulation environment is modified. The simulation environment can place the practice of technical skills in a range of contexts, from the use of portable trainer at home[43] to a completely simulated operating theatre containing a theatre team[44]. What is being taught and assessed during the simulation is, therefore, highly dependent on the simulation environment.

One means of broadening the scope of endoscopic simulation is to place an actor within the simulation environment, producing a "simulated patient". This simulation demands more of the learner than the simple performance of a technical task, as the interaction with the simulated patient must occur alongside the simulated endoscopic procedure[45-47]. Kneebone *et al*[48] describe a course for novice nurse endoscopists in which a component is the use of "hybrid simulation" in which an actor and a VR simulator are combined. These authors achieved this by setting up the room with the actor leaning on their left side next to the simulator, with a blanket covering both, producing the illusion that the procedure was being carried out on a real patient. This course led to an improvement in simulator metrics from the VR simulator, and extremely positive qualitative feedback about the improvement in communication skills facilitated by the use of simulated patients.

Another example of using the simulation environment to broaden the scope of simulation is the placement of a simulator within the normal clinical environment, achieving a degree of fidelity that is not usually achievable, unlocking the potential of simulation to reveal interactions within clinical teams as well as between clinicians and patients.

Finally, the use of a portable space for simulation as a simulation environment has the potential to avoid both the problem of simulation being inaccessible to trainees located away from central clinical skills centres and simulation sessions disturbing the normal function of the clinical environment. This has been described by a group from Imperial College London using an inflatable environment in which a large number of simulations can be produced[49]. This space can then be filled with equipment that allows a clinical area to be simulated with enough realism to produce a high degree of fidelity, whilst being portable enough to be placed in a car.

CONCLUSION

The use of simulation to train the next generation of endoscopists needs to be supported by an increasing amount and quality of evidence, particularly for the clinical transferability of simulation training, but it is arguable that the evidence available already supports the use of simulation to train novice endoscopists.

The technology available for simulators is likely to lead to an increase in fidelity and to an increase in the complexity of metrics available, and validity studies supporting the use of each new generation of simulators is important both to support their use for training and also, in particular, to support their use for assessment.

We would argue that further thought also needs to be given to the simulation environment. Increasing the sophistication of simulation by manipulating the simulation environment, as we have seen, contains the potential to address the teaching of skills beyond the technical.

Further work is needed to place simulation within a broader curriculum of training. The majority of studies looking at simulation in endoscopy have looked at the effect of short periods of simulation training before clinical experience. It may be that integration of simulation alongside developing clinical practice might increase its efficacy and lead to a more sustained benefit than those demonstrated by studies to date.

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ORIGINAL ARTICLE

Monitoring salivary amylase activity is useful for providing timely analgesia under sedation

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Abstract

AIM: To detect the criteria and cause of elevated salivary amylase activity (sAMY) in patients undergoing endoscopic submucosal dissection (ESD) under sedation.

METHODS: A total of 41 patients with early gastric cancer removed *via* ESD under deep sedation (DS) were enrolled. The perioperative sAMY, which was shown as sympathetic excitements (SE), was measured. The time at which a patient exhibited a relatively increased rate of sAMY compared with the preoperative baseline level (IR, %) ⩾ 100% (twice the actual value) was assumed as the moment when the patient received SE. Among the 41 patients, we focused on 14 patients who exhibited an IR ⩾ 100% at any time that was associated with sAMY elevation during ESD (H-group) and examined whether any particular endoscopic procedures can cause SE by simultaneously monitoring the sAMY level. If a patient demonstrated an elevated sAMY level above twice the baseline level, the endoscopic procedure was immediately stopped. In the impossible case of discontinuance, analgesic medicines were administered. This study was performed prospectively.

RESULTS: A total of 26 episodes of sAMY eruption were considered moments of SE in the H-group. The baseline level of sAMY significantly increased in association with an IR of > 100% at 5 min, with a significant difference (IR immediately before elevation/IR at elevation of sAMY = 8.72 ± 173/958 ± 1391%, $P < 0.001$). However, effective intervention decreased the elevated sAMY level immediately within only 5 min, with a significant difference (IR at sAMY elevation/immediately after intervention = 958 ± 1391/476 ± 1031, $P < 0.001$). The bispectral indices, systolic blood pressure and pulse rates, which were measured at the same time, remained stable throughout the ESD. Forceful endoscopic insertion or over insufflation was performed during 22 of the 26 episodes. Release of the gastric wall tension and/or the administration of analgesic medication resulted in the immediate recovery of the elevated sAMY level, independent of body movement.

CONCLUSION: By detecting twice the actual sAMY based on the preoperative level, the release of the gastric wall tension or the administration of analgesic agents should be considered.

Key words: Salivary amylase activity; Endoscopic sub-

mucosal dissection; Analgesia; Anesthesia; Sedation; Sympathetic excitement; Gastric wall tension

Core tip: The analgesia in patients during endoscopic submucosal dissection (ESD) under deep sedation (DS) has not yet been developed. There was no way of measuring the degree of the pain in those patients. This study revealed that the salivary amylase activity (sAMY) shown as sympathetic excitement (SE) sometimes was elevated during ESD without any change in circulatory dynamics or consciousness. We suggest that sAMY is elevated when patients feel pain during ESD under DS. By detecting twice the actual sAMY based on the preoperative level, the release of gastric wall tension or the administration of analgesic agents should be considered.

Uesato M, Nabeya Y, Akai T, Inoue M, Watanabe Y, Horibe D, Kawahira H, Hayashi H, Matsubara H. Monitoring salivary amylase activity is useful for providing timely analgesia under sedation. *World J Gastrointest Endosc* 2014; 6(6): 240-247 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i6/240.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i6.240

INTRODUCTION

Endoscopic submucosal dissection (ESD) is widely used to treat early gastric cancer because the *en bloc* resection of lesions *via* ESD provides a detailed pathological assessment and possible radical cure[1-4]. However, technical difficulties and the expanded eligibility criteria for ESD can also result in a prolonged procedure time[1,5,6], and ESD is generally performed under deep sedation (DS)[7,8]. Accordingly, there is an increased risk of anesthesia-related complications that are associated with higher doses of sedative drugs as more opportunities to perform ESD for gastric tumors arise[9]. The effect of analog-sedation for the patients in the intensive care unit has recently attracted attention. Egerod *et al*[10] recommends an interdisciplinary effort to target patients requiring less because issues of oversedation and inadequate pain management still require additional attention. In addition, the administration of additional analgesics can stabilize the condition of patients under sedation during endoscopic procedures[11]. Consequently, providing timely and adequate analgesia in addition to sedation for the entire duration of ESD is essential. Several methods can be used to determine the state of the consciousness in patients, including the bispectral index monitor designed by Aspect Medical Systems (Norwood, MA, United States) and the Ramsey sedation score. However, a method for measuring analgesic degree has not yet been developed. In practice, endoscopists administer analgesics to patients during ESD without following specific criteria.

The salivary amylase activity (sAMY) is controlled by epinephrine secreted from the adrenal medulla, which is caused by enhanced activity of the sympathetic-nervous-adrenomedullary system[12,13]. Recent studies have demonstrated the efficacy of assessing psychological stress objectively by monitoring sAMY[14,15], and an instrument using this method to assess stress with rapidity and low invasiveness has been marketed for practical use[16,17]. We have already reported that using this instrument, the analgesic level can be monitored easily and accurately according to the sAMY level, which may positively contribute to performing safe and secure ESD under DS[18]. Hence, we first disclosed that monitoring the sAMY level can be used to objectively assess stress in response to pain in patients undergoing ESD[18].

As a next step, two aims of this study are to detect the sAMY level, which can be shown as a significant sympathetic excitement (SE) in patients undergoing ESD for gastric tumors under DS, and to explore which particular endoscopic surgery techniques cause a significant SE.

MATERIALS AND METHODS

This study enrolled 41 consecutive patients with early gastric cancer who were treated at the Department of Frontier Surgery or the Department of Endoscopic Diagnostics and Therapeutics, Chiba University Hospital. The patients underwent ESD under properly maintained DS with midazolam (0.04-0.06 mg/kg *iv*) or propofol (1-2 mg/kg *iv*) and pentazocine (7.5 mg *iv*); neither anticholinergic nor vasopressive agents were used. Carbon dioxide was used in the insufflation of the endoscope.

The sAMY levels were determined as previously reported[18]. Briefly, we measured the sAMY level using enzyme analysis equipment, a sAMY Monitor (NIPRO Co., Osaka, Japan), prior to performing ESD in the morning, immediately following the induction of sedation, and every five minutes after the initiation of ESD. sAMY measurement requires only 1 min after saliva sampling under the tongue. We evaluated the intraoperative sAMY value by calculating the relative rate of increase in the sAMY level compared with the control level (IR, %) as follows: (the elevated sAMY level-the baseline level prior to ESD in the morning)/the baseline level × 100. According to the results of our previous study[18], the median (range) of IR was 105.2% (1.7-3050). Taken together, in this study, we assumed the time when a patient exhibited an IR of $\geqslant$ 100% (twice the actual value) as the moment when the patient received SE. This study was performed prospectively. In addition, we simultaneously monitored the endoscopic procedures and the perturbation of the sAMY level and examined which techniques were associated with SE during ESD. However, completing ESD as soon as possible was more important than exploring the possible causes of SE. Similar to the case in a previous report[18], intense body movement occurred in a patient after a high sAMY level was overlooked. Therefore, if a patient appeared to a high sAMY level during ESD, the operator attempted to remove the source of the SE immediately and not to overlook it.

Fourteen patients who exhibited an IR of $\geqslant$ 100%

Table 1 Patient characteristics

	H-group	M-group	L-group	*P* value
No. of patients	14	8	19	
Gender (male/female)	9/5	6/2	16/3	0.429
Age (yr)	71.5 ± 11.7	71.6 ± 8.9	69.9 ± 7.0	0.569
(range)	(40-84)	(58-86)	(58-81)	
Body weight (kg)	57.3 ± 10.6	62.4 ± 10.0	58.8 ± 8.7	0.443
(range)	(43.1-82)	(49-80.3)	(44-76)	
No. of tumors	14	8	19	
Location U/M/L	1/5/8	0/2/6	3/6/10	0.464
Less, post/great, ant	9/5	3/5	10/9	0.485
Resected tumor size (mm)	29.0 ± 10.0	29.3 ± 12.7	30.2 ± 11.4	0.827
(range)	(15-49)	(17-58)	(12-50)	
Procedure time (min)	78.0 ± 54.1	92.5 ± 55.9	73.7 ± 46.8	0.717
(range)	(35-240)	(35-200)	(20-205)	

The data are presented as the mean ± SD. U: Upper third of the stomach; M: Middle third of the stomach; L: Lower third of the stomach; Less: Lesser curvature; Great: Greater curvature; Ant: Anterior wall; Post: Posterior wall.

at any time associated with sAMY elevation during ESD were categorized into the H-group. Nineteen patients who failed to exhibit an IR of ≥ 100% at any time associated with sAMY elevation during ESD were categorized into the L-group. The remaining eight patients exhibited various IR values and were categorized into the M-group. When a patient demonstrated an elevated sAMY level during ESD, the endoscopic procedure was immediately stopped. In the impossible case of discontinuance, analgesic medicines were administered. Therefore, we calculated the recovery rate of sAMY (%) as follows: (the elevated sAMY level-the decreased sAMY level immediately following intervention)/the elevated sAMY level × 100. We defined a forceful endoscopic insertion when the tip of the endoscope was inserted more than 80 cm from the incisor line to stomach and an over insufflation when the gastric fold completely disappeared.

The patient's blood pressure and pulse rate were also assessed at the time of sAMY measurement. In addition, a bispectral index monitor was used to evaluate the level of consciousness. All patients were interviewed using a questionnaire prior to discharge to determine their subjective consciousness level.

The institutional review board approved the study protocol, and written informed consent was obtained from all patients before enrollment.

Statistical analysis

Continuous data are presented as the mean ± SD. The Mann-Whitney *U* test was used to analyze the differences in continuous or ordinal variables between the groups. Fisher's exact test was used to evaluate the differences in proportions between the groups, and the Kruskal-Wallis test was used in proportion among the three groups. Perioperative changes in the IR values around the moment of sAMY elevation were compared using the Wilcoxon signed rank-sum test. All statistical analyses were conducted using the SPSS 15.0 software package (SPSS Inc., Chicago, IL, United States). *P* values of less than 0.05 were considered to be statistically significant.

Table 2 Body movement during salivary amylase activity elevation

	H-group	M-group	L-group	*P* value
No. of patients	14	8	19	
No. of elevated sAMY (times)	26	30	16	
≥ twice the actual value	26	11	0	
< twice the actual value	0	19	16	
with body movement	17	16	6	0.215 ([1]0.078)
without body movement	9	14	10	

[1]Indicates a comparison between the H- and L-groups. sAMY: Salivary amylase activity.

RESULTS

The patient characteristics are shown in Table 1. No significant differences were observed among the three groups in terms of clinical characteristics, including the procedure time. The H-group demonstrated 26 episodes of sAMY elevation (with an IR of ≥ 100%). The M-group exhibited 30 episodes of sAMY elevation (11 episodes of an IR of ≥ 100% and 19 episodes of an IR of < 100%), and the L-group exhibited 16 episodes of sAMY elevation (with an IR of < 100%). The number of episodes of an elevated sAMY level associated with body movement was higher in the H-group than it was in the L-group ($P = 0.078$) (Table 2). However, even in the H-group, nine (34.6%) of the 26 episodes of an elevated sAMY (with an IR of ≥ 100%) were not accompanied by simultaneous body movement. The method of sedation failed to affect the sAMY level immediately after the induction of sedation (midazolam/propofol = 39.70 ± 49.18/29.26 ± 44.62 KU/L, $P = 0.926$). All 41 patients responded with "I did not wake up at all" on the post-ESD questionnaire.

In this study, because we aimed to explore the relationships among the sAMY elevation associated with SE, the patients' condition, and the endoscopic procedure, we focused on the patients in the H-group, who were considered to experience the potential pain at any time of sAMY elevation during ESD compared with the patients in the "painless" L-group. Figure 1 shows the variation in the IR and bispectral index associated with the 26 episodes of sAMY elevation in the H-group. The baseline level of sAMY significantly increased in association with an IR of > 100% at 5 min, with a significant difference (IR immediately before elevation/IR at sAMY elevation = 8.72 ± 173/958 ± 1391%, $P < 0.001$). However, an effective intervention decreased the elevated sAMY level immediately within only 5 min, with a significant difference (IR at sAMY elevation/immediately after intervention = 958 ± 1391/476 ± 1031, $P < 0.001$). The bispectral indices in the patients undergoing ESD proved to be stable throughout the procedures, even when the sAMY

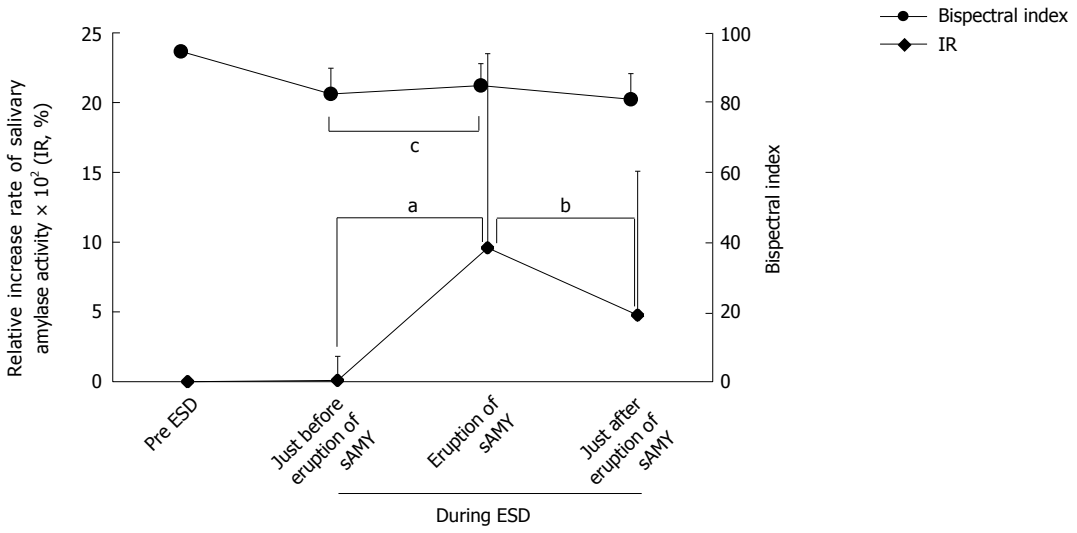

Figure 1 Changes in the relative rate of increase of the salivary amylase activity level compared with the control level, salivary amylase activity (IR, %), and the bispectral index around the 26 episodes of salivary amylase activity elevation in the H-group. The baseline level of sAMY significantly increased in association with an IR of > 100% at only 5 min, with a significant difference (IR immediately before elevation/IR at elevation of sAMY = 8.72 ± 173/958 ± 1391%, [a]*P* < 0.001). However, the release of gastric wall tension and/or pentazocine injection effectively decreased the elevated sAMY level immediately within only 5 min with a significant difference (IR at sAMY elevation/immediately after intervention = 958 ± 1391/476 ± 1031, [b]*P* < 0.001). The bispectral indices in the patients undergoing ESD proved to be stable throughout the procedures ([c]*P* = 0.272), even when the sAMY level was elevated in association with an IR of > 100%, *i.e.*, when the patient received SE. All 14 patients responded with "I did not wake up at all" on the post-ESD questionnaire. The data are presented as the mean ± SD. ESD: Endoscopic submucosal dissection; DS: Deep sedation; sAMY: Salivary amylase activity; SE: Sympathetic excitement; H-sAMY: A high value of salivary amylase activity; L-sAMY: A low value of salivary amylase activity.

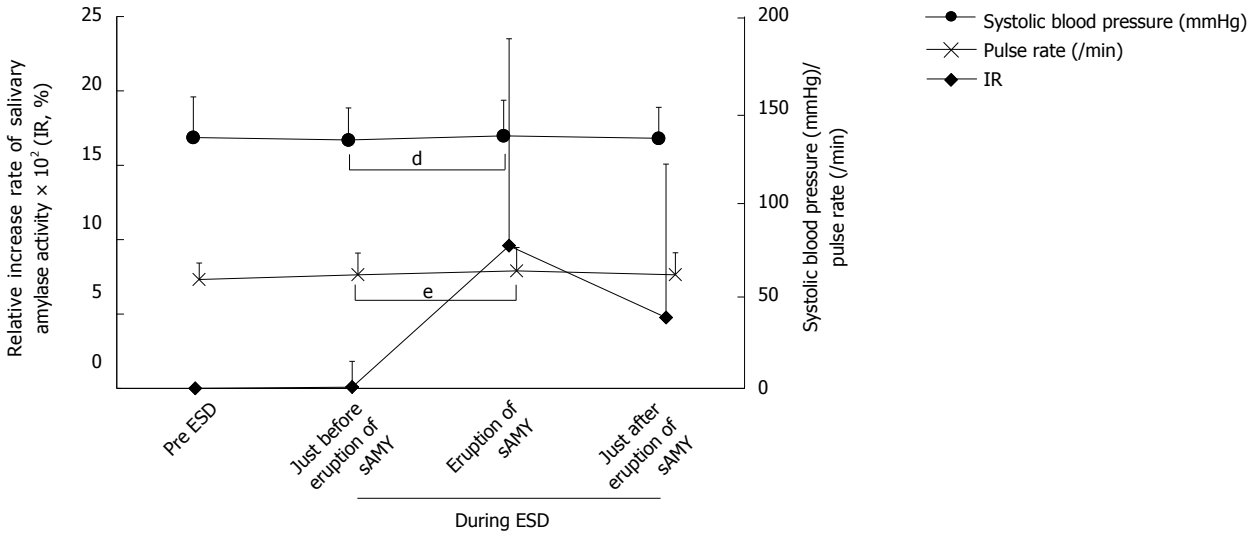

Figure 2 Changes in the relative rate of increase of the salivary amylase activity level compared with the control level, salivary amylase activity (IR, %), the systolic blood pressure (mmHg) and pulse rate (/min) around the 26 episodes of salivary amylase activity elevation in the H-group. The values of systolic blood pressure and pulse rate also remained stable during ESD, regardless of the change in the sAMY ([d]*P* = 0.660 and [e]*P* =0.614, respectively). The data are presented as the mean ± SD. ESD: Endoscopic submucosal dissection; DS: Deep sedation; sAMY: Salivary amylase activity; SE: Sympathetic excitement; H-sAMY: A high value of salivary amylase activity; L-sAMY: A low value of salivary amylase activity.

level was elevated in association with an IR of > 100%, *i.e.*, when the patient received SE (Figure 1). Figure 2 shows the variations in systolic blood pressure and pulse rate that were associated with perturbation in the IR in the H-group. The systolic blood pressure values and pulse rates were also stable throughout ESD. The status of simultaneous body movement did not significantly affect the IR in the H-group, while the IR values that were not associated with body movement (nine episodes) were relatively higher than those associated with body movement (17 episodes) (Figure 3, *P* = 0.236).

The technical status at the moment of sAMY elevation was compared between the H- and L-groups (Table 3). In both groups, the most frequent operative technique was "Dissection" (H-group/L-group; 11/26 = 42.3%/10/16=62.5%), and no significant differ-

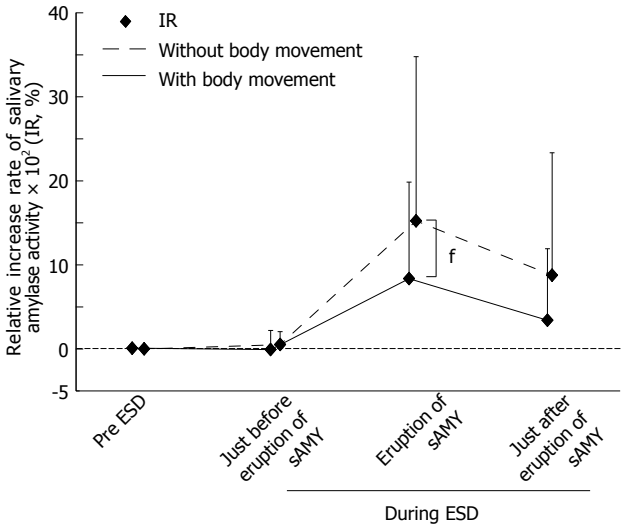

Figure 3 Changes in the relative rate of increase of the salivary amylase activity level compared with the control level, salivary amylase activity (IR, %), with reference to the status of body movement in the H-group. The levels of IR that were not associated with body movement (9 episodes) were relatively higher than those associated with body movement (17 episodes); however, no significant differences were observed ($^{f}P = 0.236$). The patients received SE shown as the elevation of sAMY, even if they were unconscious and exhibited no body movement. The management of the sAMY might prevent the patient's body movement that may occur in the near future. The data are presented as the mean ± SD. ESD: Endoscopic submucosal dissection; DS: Deep sedation; sAMY: Salivary amylase activity; SE: Sympathetic excitement; H-sAMY: A high value of salivary amylase activity; L-sAMY: A low value of salivary amylase activity.

ences were found in the frequency of this technique ($P = 0.430$). "Inversion" was the most frequent direction (H-group/L-group; 14/26 = 53.8%/10/16, 62.5%) in both groups, without significant intergroup differences in the frequency of this direction ($P = 0.582$). Forceful endoscopic insertion or over insufflation were performed during 22 of the 26 episodes (84.6%) of sAMY elevation in the H-group; the frequency of these procedures was significantly higher in the H-group than it was in the L-group (56.3%, $P = 0.042$). The interventions used to treat sAMY elevation, which indicated SE, in the H-group are shown in Table 4. To relieve SE immediately, either release of gastric wall tension or pentazocine injection were performed during the 14 episodes of sAMY elevation associated with body movement. In two cases, both technical and medical interventions (*i.e.*, release of gastric wall tension and medication administration) were concomitantly performed. The recovery rate of a sAMY elevation that was not associated with body movement did not significantly differ from that of a sAMY elevation that was associated with body movement. Midazolam or propofol were administered in only two patients with high bispectral indices and were very effective in both cases.

DISCUSSION

The results of this study first demonstrated that the gastric wall tension caused by forceful endoscopic insertion or over insufflation is a major cause of SE in patients undergoing ESD for gastric tumors under DS. A link between SE and the status of the endoscopic procedure was clearly shown by monitoring the sAMY level, which objectively reflects the analgesic level in unconscious gastric ESD patients. The management of the sAMY might prevent the unanticipated body movement in patients during ESD.

Kiriyama *et al*[19] reported that local lidocaine injections into the submucosal layer are effective for local pain control both immediately after and during ESD, because local pain can be caused by the formation of artificial gastric ulcers. In their study, the level of pain and the effects of lidocaine during surgery were evaluated indirectly based on the reduced total dose of pentazocine[19]. However, our current study demonstrated that an IR of sAMY ⩾ 100%, which indicates intraoperative SE, was not always observed, although every patient suffered from artificial ulcers induced by ESD. Moreover, there were no significant differences between the H- and L-groups in terms of the size of the resected tumors. Therefore, the degree of SE demonstrated by the sAMY level may not necessarily depend on ulcer formation, and the size of an artificial ulcer may not be crucial for SE, at least in patients undergoing gastric ESD. This idea is supported by our experience, as most patients who are conscious do not feel pain when they are treated with gastric

Table 3 Technical status during salivary amylase activity elevation

	H-group	L-group	*P* value
No. of elevated sAMY (times)	26	16	
Operative techniques			
Incision	9	4	0.430
Dissection	11	10	
Hemostasis	6	2	
Endoscopic direction			
Straight	12	6	0.582
Inversion	14	10	
Forceful endoscopic insertion or over insufflation			
Presence	22	9	0.042
Absence	4	7	

sAMY: Salivary amylase activity.

Table 4 Interventions used to treat salivary amylase activity elevation and the improvement in terms of body movement [number of episodes of salivary amylase activity elevation/ recovery rate of salivary amylase activity (%)]

Body movement	Presence	Absence
Number (times)	17	9
Release of gastric wall tension only	2/86.2	5/66.1
Medication (pentazocine injection) only	12/94.7	3/95.9
Release and medication (pentazocine)	2/119.6	0/-
Medication (midazolam or propofol injection) only	1/124.2	1/85.6

Recovery rate of sAMY (%) = (the elevated sAMY level-decreased sAMY level immediately after intervention)/the elevated sAMY level × 100. sAMY: Salivary amylase activity.

or colonic endoscopic mucosal resection. We therefore hypothesized that the operative time or some particular technique of the operative procedure, which varies among individuals, is associated with the development of SE in patients undergoing gastric ESD.

Our data suggest that the development of SE during gastric ESD is not related to a long operative time (Table 1). However, we found that the status of forceful endoscopic insertion or over insufflation significantly differed between the H- and L-groups (Table 3). Regarding the sudden production of sAMY, sympathetic fibers directly trigger the salivary gland, which secretes amylase before the gland responds to norepinephrine from the adrenal medulla[20]. In the current study, the systolic blood pressure values and pulse rates remained stable, even when the sAMY level suddenly changed during gastric ESD. Most likely, an increased sAMY level reflects sympathetic nerve excitement before circulatory dynamics become unstable. If the endoscopic procedures were to be subsequently continued, the sympathetic nerves would be further excited, and the blood pressure and pulse rate would become unstable. In this study, we successfully demonstrated this relationship by monitoring the sAMY level, which reflects the degree of potential pain during gastric ESD under DS and proper interventions.

Sensory receptors (mechanoreceptors) that are present in the mucosa, musculature (bowel wall), serosal surface, and mesentery[21-23] primarily respond to mechanical events, such as distension, torsion, contraction, and compression or stretching of the gut[23]. According to basic science experiments, gastric and/or colorectal distention induces acute visceral pain[24,25]. In particular, colorectal distension in rats stimulates cardiovascular and visceromotor responses[25]. Moreover, both morphine and clonidine produce a dose-dependent inhibition of cardiovascular and visceromotor responses to colorectal distension[25]. Clinically, the degree of discomfort a patient feels during a colonoscopic examination varies considerably and is related to the force imparted on the colon by the colonoscopy instruments, stretching the colonic wall, and mesenteric attachments, causing excessive gaseous insufflation[26,27]. These previously reported findings are consistent with the results of our gastroscopy study. However, there have been no such reports on the link between the objective evaluation of pain, *i.e.*, measurement of the sAMY level, and the technical status during gastric ESD. If ESD is performed under steady pressure automatically controlled endoscopy[28], we might reveal more clinical details of the relationship between the pain and the over insufflation.

While assessing and measuring pain are very important considerations for both patients and physicians, as previously described[19], pain tolerance varies greatly among individuals. Accordingly, the results of our study are significant with respect to the individualized, safe management of patients who undergo ESD for gastric tumors under DS. First, the operator should avoid causing gastric wall tension to relieve intraoperative pain. However, if releasing gastric wall tension cannot be achieved due to necessary technical steps or if it is not effective at reducing the patient's pain, analgesic drugs, such as pentazocine, should be administered immediately. These results support the findings of a previous report showing that morphine produces a dose-dependent inhibition of visceromotor responses to colorectal distension in rats[25]. In addition, in our study, analgesic evasion resulted in a significant decrease in the sAMY level within only 5 min.

Until recently, ESD operators have typically used body movement to indicate the moment that a patient feels pain during ESD performed under DS. However, it is important to note that 34.6% of the patients in the H-group exhibited no body movement in our study. This result suggests that, when sAMY elevation indicating pain is observed, analgesic drugs should be administered immediately to decrease the pain, even in patients without body movement. If the sAMY elevation is overlooked, significant variations in systolic blood pressure, pulse rate, and body movement will occur. Therefore, an elevation of the sAMY level is a timely, practical, and objective indicator of intraoperative pain during gastric ESD, even when the patient fails to move simultaneously. The incidence of complications, such as bleeding or perforation, increases if the patient moves during ESD. It is therefore clinically important to address pain before movement occurs. In this study, we focused on the patients in the H-group, who were considered to experience potential pain at any time of sAMY elevation during ESD, compared with the patients in the "painless" L-group. However, the degree of sAMY elevation varied among the patients. Therefore, to safely complete gastric ESD, continuously monitoring the sAMY level throughout the ESD procedure is advisable to accurately assess the real-time degree of pain in individual patients and to determine when to release endoscopic stretching or appropriately administer analgesics after detecting twice the actual sAMY based on the preoperative value.

In this study, even when an elevated sAMY level was observed in the patients undergoing ESD, the average bispectral index was stable (Figure 1). Furthermore, all patients responded with "I did not wake up at all" on the post-ESD questionnaire. Midazolam and/or propofol injection was effective in two patients with both high bispectral indices and high sAMY elevation levels (one case without body movement) in the H-group. High levels of both the bispectral index and sAMY suggest that a patient may be in a waking state. Accordingly, monitoring the sAMY level simultaneously with the bispectral index enables physicians to differentially understand the levels of pain and consciousness in patients undergoing gastric ESD under DS and is of great clinical significance.

In conclusion, pain, as represented by twice the actual sAMY based on the preoperative level, in unconscious patients undergoing ESD under DS for gastric tumors may be caused by the gastric wall tension, which can elevate the sAMY level quickly, even without body move-

ment, before a change in cardiovascular response. Therefore, continuously monitoring the changes in the sAMY level and either modifying the endoscopic technique or administering analgesics can be used to treat pain in a timely manner, and patients undergoing ESD for gastric tumors under DS can be managed more securely.

COMMENTS

Background

Endoscopic submucosal dissection (ESD) is widely used to treat early gastric cancer under deep sedation (DS) and analgesia. Accordingly, there is an increased risk of anesthesia-related complications associated with higher doses of sedative and analgesic drugs as the opportunities to perform ESD for gastric tumors arise. There are several methods to know the state of the consciousness in patients. However, a method to measure analgesic degree has not yet been established.

Research frontiers

Recent studies have demonstrated the efficacy of assessing psychological stress objectively by monitoring salivary amylase activity (sAMY), and an instrument using this method to assess stress with rapidity and low invasiveness has been marketed for practical use.

Innovations and breakthroughs

Until recently, ESD operators have usually judged body movement to indicate the moment that a patient feels discomfort during ESD performed under DS and given the analgesics to patients without criteria. The authors aimed to detect the criteria of sAMY level shown as a significant sympathetic excitement in patients undergoing ESD of gastric tumors under DS and to explore which particular techniques of endoscopic surgery cause the sAMY elevation.

Applications

The study results suggest that by detecting twice the actual sAMY based on the preoperative level, the release of gastric wall tension or the administration of analgesic agents should be considered.

Terminology

sAMY: salivary amylase activity is controlled by epinephrine secreted from the adrenal medulla, caused by enhanced activity of the sympathetic nervous-adrenomedullary system.

Peer review

In this manuscript, Uesato *et al* provided a novel way to measure the depth of analgesia by a quantitative marker. This manuscript is interesting.

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RETROSPECTIVE STUDY

Predictors of double balloon endoscopy outcomes in the evaluation of gastrointestinal bleeding

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Abstract

AIM: To identify patients' characteristics associated with double balloon endoscopy (DBE) outcomes in investigation of obscure gastrointestinal bleeding (OGIB).

METHODS: Retrospective study performed at an academic tertiary referral center. Evaluated endpoints were clinical factors associated with no diagnostic yield or non-therapeutic intervention of DBE performed for OGIB evaluation.

RESULTS: We included fifty-five DBE between August 2010 and April 2012. The mean age of the sample was 67 with 32 males (58.2%). Twenty-four DBE had no diagnostic yield and 30 DBE did not require therapy. Non-diagnostic yield was associated with performing two or more DBE studies in one day [odds ratio (OR): 13.72, P = 0.008], absence of blood transfusions within a year of the DBE (OR: 7.16, P = 0.03) and absence of ulcers or arteriovenous malformations (AVMs) on prior esophagogastroduodenoscopy (EGD) or colonoscopy (OR: 19.30, P = 0.033). Non-therapeutic DBE was associated with performing two or more DBE per day (OR: 18.579, P = 0.007), gastrointestinal bleeding episode within a week of the DBE (OR: 11.48, P = 0.003), fewer blood transfusion requirements prior to DBE (OR: 4.55, P = 0.036) and absence of ulcers or AVMs on prior EGD or colonoscopy (OR: 8.47, P = 0.027).

CONCLUSION: Predictors of DBE yield and therapeutic intervention on DBE include blood transfusion requirements, previous endoscopic findings and possibly endoscopist fatigue.

Key words: Double balloon endoscopy; Enteroscopy; Obscure gastrointestinal bleeding; Small bowel; Anemia; Arteriovenous malformations; Arteriovenous malformations

Core tip: Double balloon endoscopy (DBE) is an excellent tool to visualize the small bowel and provide treatment. However, it may be unable to identify a source for bleeding in 20% to 40% of obscure gastrointestinal bleeding (OGIB) cases. This small retrospective case-control study showed that factors such as fewer blood transfusion requirements, absence of arteriovenous malformations or ulcers on prior endoscopies and possibly endoscopist fatigue may predict a negative diagnostic and therapeutic yield of DBE. This may help manage patients with OGIB and multiple comorbidities and potentially reduce health care costs by classifying patients who are most likely to

benefit from this time intensive procedure.

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INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) is defined as persistent or recurrent gastrointestinal hemorrhage for which no definite source has been identified by esophagogastroduodenoscopy (EGD) or ileocolonoscopy. It accounts for approximately 5% of all cases of gastrointestinal bleeding[1]. It can present as overt bleeding, or without visible blood but signs of iron deficiency anemia suggestive of a gastrointestinal source.

OGIB is a dilemma for gastroenterologists. It often requires multiple endoscopies[2]. Push enteroscopy, small bowel follow-through, radionuclide scanning, and angiography have had variable success in this setting[3,4]. Traditionally, intraoperative enteroscopy has been the only method available for complete small bowel evaluation. However, because of its increased morbidity and mortality compared to wireless capsule endoscopy and device assisted small bowel enteroscopy, it has decreased in popularity[5].

Video capsule endoscopy (VCE) is safe, simple and has a high sensitivity in evaluation of small bowel lesions. It is however limited in its ability to obtain tissue for histology and to provide endoscopic therapy[5]. Double-balloon endoscopy (DBE) was first introduced by Yamamoto *et al*[6] in 2001. In contrast to push enteroscopy and wireless capsule endoscopy, DBE can potentially visualize the entire small bowel and offers therapeutic potential[7-9]. Wireless capsule endoscopy and double balloon endoscopy provide similar diagnostic yield and have satisfactory concordance rate in the evaluation of OGIB[10,11].

DBE is associated with a relatively low complication rate profile of 1.2%[12]. Suspected small bowel bleeding is the main indication for DBE[7]. However, DBE may be unable to identify a source for bleeding in 20% to 40% of OGIB cases[13-16]. DBE is also time-consuming and labor-intensive, with an average examination time of approximately 60 to 90 min[8,13]. Identifying patients with a higher probability of successful detection and therapy of bleeding sources with DBE is important for resource utilization. Our study investigates factors that may predict negative findings on double balloon endoscopy based on clinical, laboratory and endoscopic findings.

MATERIALS AND METHODS

Study patients

We retrospectively reviewed patients referred to Saint Louis University Hospital for double balloon endoscopy between August 1, 2010 and April 6, 2012. Inclusion criteria included 18-80 years old patients who underwent double balloon endoscopy for OGIB.

Review of medical records

The medical records of all patients who met inclusion criteria were reviewed. Data collected included demographics, clinical, laboratory and endoscopic data. This study was approved by the institutional review board at Saint Louis University.

Endoscopists

Two experienced endoscopists performed all the DBE procedures. The endoscopists received dedicated training in balloon endoscopy through an ASGE course and initial case monitoring by an expert in the field.

DBE procedure

Informed consent was obtained prior to all DBE procedures. The DBE system (Fujinon, Inc., Saitama, Japan) was utilized. Initial approach with anterograde double balloon endoscopy was performed if capsule findings were within the proximal two third of small bowel, rectal approach if findings were more distal in the small intestine. We used the standard DBE method for insertion, withdrawal and observation, as described previously[17]. For anterograde DBE, patients were kept nothing by mouth (NPO) at least 8 h prior to procedure and no particular bowel preparation was given. For retrograde DBE, bowel preparation with 4 L polyethylene glycol was used. Monitored anesthesia care with intravenous propofol, administered by staff anesthesiologists was used for most cases. Midazolam and narcotics were added occasionally to optimize sedation at the discretion of the anesthesiologist. Spot ink tattoo was placed to mark the maximum insertion depth reached. The small bowel segment suspected to have pathology on VCE was carefully inspected. The opposite route was used if pathology was not reached with the initial insertion route as deemed clinically appropriate.

Classification

Active gastrointestinal (GI) bleeding at the time of DBE was defined as overt bleeding within one week from DBE while non-active GI bleeding was defined as overt bleeding beyond one week from DBE. Acute GI bleeding was defined as GI bleeding within one month from VCE or DBE. Positive diagnostic yield on DBE was defined as cases with significant endoscopic findings [ulcers, arteriovenous malformations (AVMs), ulcerated masses or polyps] consistent with patients' clinical presentation and/or VCE findings. Therapeutic yield on DBE was defined as cases in which endoscopic intervention was performed. Positive findings on capsule endoscopy were defined as either the visualization of a lesion (AVMs, ulcerated polyps, mass, ulceration, multiple erosions) or the presence of blood and/or blood clots in the lumen of the small bowel. Negative or nonspecific capsule findings were assigned when an investigation showed no ab-

Table 1 Double balloon endoscopy findings

Findings	*n* (%)
AVM	20 (36.4)
Ulcer	3 (5.5)
Ulcerated polyp	3 (5.5)
Ulcerated mass	1 (1.8)
Multiple erosions	2 (3.6)
Portal HTN enteropathy	1 (1.8)
Vascular polyp	1 (1.8)
Negative findings	24 (43.6)

AVM: Arteriovenous malformation.

Table 2 Bivariate analysis of negative diagnostic double balloon endoscopy

Variables	Negative diagnostic yield	No therapeutic intervention
Pre-DBE ASA score ≤ 2	0.611	0.044
GI bleed within 1 wk prior to DBE	0.179	0.010
Blood transfusions ≤ 4 units 10 yr prior to DBE	0.149	0.027
> 1 DBE in one day by single endoscopist	0.016	0.024
Hgb > 9 mg/dL in the week prior to DBE	0.010	0.035
No blood transfusions in the year prior to DBE	0.019	0.044
Prior EGD with no ulcers or AVMs	0.031	0.004
Prior EGD or colonoscopy with no ulcers or AVMs	0.001	0.001
Prior enteroscopy with no AVMs	0.013	0.009

DBE: Double balloon endoscopy; GI: Gastrointestinal; EGD: Esophagogastroduodenoscopy; AVM: Arteriovenous malformation.

normalities or showed nonspecific findings (isolated red spots or single erosion). Endoscopic hemostasis by argon plasma coagulation, electrocoagulation, or clipping was used for vascular lesions. Ulcers were treated if they were actively bleeding or had visible bleeding vessels. Small polyps were removed and tumors were generally tattooed and biopsied for histopathology.

Statistical analysis

SPSS software (Version 20 SPSS Inc., Chicago) was used to collect and analyze the data. Descriptive statistics, chi square, Fisher's exact test and logistic regression were conducted to analyze and identify variables associated with negative findings or no therapy during DBE. A P value < 0.05 was considered to be statistically significant.

RESULTS

A total of 55 DBE cases were reviewed. The mean age of the sample was 67.4 ± 11.2 years old with 32 men (58.2%). The majority of patients with overt GI bleeding presented with melena (30 cases, 54.5%), whereas 9 (16.4%) presented with hematochezia. An additional 5 cases presented with both (9%). The majority of patients had chronic GI bleeding of more than 1 mo duration (75.5%). The mean lowest hemoglobin was 7.42 ± 2.16 mg/dL in the 5 years prior to DBE.

A total of 13 cases were missing prior EGD or colonoscopy official reports. Push enteroscopy was performed on 23 cases prior to DBE and most procedures had preceding VCE (96.4%). 83.6% of cases had positive findings on VCE. However only 54.3% of positive VCE led to significant DBE findings. Presence of AVMs or active bleeding on VCE were noted on DBE in 65% of cases. Ulcers on VCE were only found in half of the follow up DBE cases. Polyps on VCE led to the lowest DBE yield (22%). Also, 5 cases had positive DBE findings that were not seen on VCE. The missed lesions were AVMs, ulcers, an ulcerated hamartoma and carcinoid tumor that led to surgery.

The mean duration of the DBE procedures was 109.8 ± 26.4 min. Fifty DBE cases (90.9%) were performed via the anterograde route. All of the anterograde DBE procedures reached the mid-distal jejunum and 35 (70%) reached the ileum. One patient had a total enteroscopy through the anterograde approach and one patient had a total enteroscopy using both oral and rectal approach.

AVMs accounted for most of our DBE findings (36.4%), as shown in Table 1. In total, 24 DBEs (43.6%) had negative diagnostic findings and 30 DBEs (54.5%) did not require endoscopic therapy. Based on our classification: 20 cases (36.4%) had active bleeding at the time of DBE, 23 (41.8%) were not active and 11 (20%) had occult GI bleeding. Positive diagnostic yield was seen in 10 (50%) active GI bleeding cases, 16 (69.5%) non-active and 4 (36.3%) occult GI bleeding cases. Five of 11 cases (45.5%) with acute GI bleeding at the time of DBE had positive diagnostic yield on DBE as opposed to 12 out 13 cases (92.3%) with acute GI bleed at the time of VCE. 4 patients required repeat DBE during our study period due to recurrent GI bleeding. Lower ASA score, negative findings on previous push enteroscopy and hgb of more than 9 prior to DBE were associated with negative diagnostic and therapeutic yield on bivariate analysis (Table 2). DBE diagnostic or therapeutic yield was not associated with age, gender, use of antiplatelets or anticoagulation medications, occult or overt bleeding, DBE procedure time, platelets, INR or albumin on bivariate analysis. Table 3 illustrates the relationship between diagnostic and therapeutic outcomes and time between GI bleed, VCE and DBE. In multivariate analysis, smaller blood transfusion requirements, absence of findings on EGD and colonoscopy and performance of more than one DBE per day per endoscopist were associated with negative diagnostic and negative therapeutic yield (Tables 4 and 5).

DISCUSSION

DBE was first described by Yamamoto *et al*[6] in 2001. Due to its potential insertion depth and total enteroscopy success, it has been an effective tool in obscure GI bleeding evaluation and management[18,19]. Previous reports indicate a 60%-80% diagnostic yield of DBE[13-16]. However, past studies have not focused on factors that may

Table 3 Time between gastrointestinal bleed, video capsule endoscopy and double balloon endoscopy in relation to outcomes *n* (%)

Variables		Less than 1 wk	1 wk to 1 mo	1 mo to 1 yr	More than 1 yr
Time from onset of GI bleed to VCE	VCE with positive findings/total No. of VCE	10/10 (100)	2/3 (66.7)	11/14 (78.6)	15/18 (83.3)
Time from onset of GI bleed to DBE	DBE with positive findings/total No. of DBE	2/8 (25)	3/3 (100)	9/14 (64.3)	17/27 (63)
	DBE leading to therapy/total No. of DBE	1/8 (12.5)	3/3 (100)	7/14 (50)	14/27 (51.9)
Time from VCE to the DBE procedure	DBEs with positive diagnostic yield/total No. of DBEs	8/15 (53.3)	3/6 (50)	15/25 (60)	3/6 (50)
	DBEs that led to therapy/total No. of DBEs	7/15 (46.7)	2/6 (33.3)	13/25 (52.0)	2/6 (33.3)

VCE: Video capsule endoscopy; DBE: Double balloon endoscopy; GI: Gastrointestinal.

Table 4 Multivariate logistic regression of factors associated with negative diagnostic yield of double balloon endoscopy

Variables	OR (95%CI)	*P* value
> 1 DBE in one day by single endoscopist	16.63 (2.04-135.45)	0.009
No blood transfusions within year prior to DBE	13.04 (1.53-111.04)	0.019
Prior EGD or colonoscopy with no ulcers or AVMs	19.30 (1.26-295.18)	0.033

DBE: Double balloon endoscopy; EGD: Esophagogastroduodenoscopy; AVM: Arteriovenous malformation.

Table 5 Multivariate logistic regression of factors associated with non-therapeutic double balloon endoscopy

	OR (95%CI)	*P* value
> 1 DBE in one day by single endoscopist	18.28 (2.24 -148.86)	0.007
GI bleed within 1 wk prior to DBE	10.77 (2.18–53.14)	0.004
Blood transfusions ≤ 4 units in the year prior to DBE	4.27 (1.03-17.71)	0.045
Prior EGD or colonoscopy with no ulcers or AVMs	8.47 (1.28-55.87)	0.027

DBE: Double balloon endoscopy; GI: Gastrointestinal; EGD: Esophagogastroduodenoscopy; AVM: Arteriovenous malformation.

help to predict outcomes of DBE.

To our knowledge, this is the first study to look at factors associated with both negative diagnostic and therapeutic yield of DBE. In the management of OGIB, patients often undergo multiple endoscopic procedures prior to DBE. The absence of findings on prior endoscopies may predict a negative diagnostic and therapeutic yield of DBE. In addition, patients with lower blood transfusion requirements were more likely to have a negative diagnostic and therapeutic yield. This is in line with what one would expect clinically and may have implications for risk stratification, utility, and timing of the procedure. Active GI bleeding in the week prior to DBE was not associated with positive DBE findings and led to less therapeutic interventions. This may be due to missed pathology on upper or lower endoscopy or due to poor visualization within the small bowel with active GI bleeding. However, most of the DBE reports did not indicate active bleeding suggesting that perhaps it is not an issue with missed pathology but a source that is no longer bleeding. This may be related to medications that are stopped while awaiting definitive therapeutic management such as anticoagulants or antithrombotics. One previous study demonstrated increased detection rates of bleeding sources on DBE for patients with two or more recurrent bleeding episodes. This was not looked at in our study[20].

Our study involved an older population undergoing DBE for obscure GI bleeding, mainly presenting with overt and chronic GI bleeding. Most of our DBE procedures were through the oral route. Small bowel AVMs were the most common findings in our study. This is consistent with previous studies where vascular lesions accounted for nearly two-thirds (65.9%) of positive findings in the western population[21]. VCE preceded DBE in 96.4% of cases. This helped guide the route and insertion depth of DBE. There was a high rate of positive VCE findings that led to non-diagnostic DBE in our study. These lesions could be classified as falsely positive VCE findings and were mainly polyps (88%), followed by ulcers (50%) and AVMs (35%). This is consistent with a previous multicenter prospective study showing acceptable concordance between DBE and VCE for AVMs and inflammatory lesions, but not for polyps or masses[11]. Protruding or bulging lesions would be falsely seen as polyps or masses on capsule endoscopy but then flattened by air insufflation when endoscopically visualized. This can explain the high rate of false positive findings for polyps. We still recommend further evaluation of polyps seen on VCE with imaging studies or endoscopy.

There are several possible reasons for negative findings on DBE. First, inability to perform complete enteroscopy in most DBE cases may limit findings. Several studies have reported widely variable rates of complete enteroscopy with DBE, ranging from 0% to 86%[7,9,13,14]. Similar to previous study designs, we relied on VCE findings to guide insertion depth and DBE insertion route. The absence of bleeding source beyond our insertion depth could not be confirmed; however our DBE cases evaluated the majority of the small intestine and reached suspected areas where positive lesions were seen on

VCE. An interesting study by Bollinger *et al*[22] using VCE to map the distribution of AVM in the western population identified the jejunum as the most common location for AVMs (80%). The ileum had the lowest distribution of AVM (5.7%)[22]. Thus, it is reasonable that the distance reached in our DBE would capture most AVMs.

Another reason for negative findings may be that lesions found on VCE may heal with time. The same number of cases had acute GI bleed at the time of VCE and DBE based on our classification of acute GI bleed, however more findings were seen with acute GI bleed at the time of VCE. This could be due to increased detection rate on VCE related to shortened time interval to onset of GI bleed. No association was found between DBE outcomes and time between VCE and DBE or time between onset of GI bleed and DBE; this could be due to a limited sample size. Third, lesions may have been missed on prior endoscopies. Fry *et al*[23] reported that a definite source of bleeding was detected in 24.3% of patients outside the small bowel and suggested that repeat upper and lower endoscopy should be considered prior to DBE. Our study only included 7 cases with repeat EGD and colonoscopy prior to DBE. Repeating endoscopy in our study did not alter findings or the need for DBE. Furthermore, an evaluation of the upper GI tract at the time of oral route DBE did not reveal any additional findings.

It is possible that negative diagnostic yield is related to missed lesions on DBE. It was hard to evaluate rebleeding rates post DBE in our study since most patients were seen at the time of DBE for the first time. However as this institution is only one of 2 referral centers in the state to perform DBE (located approximately 250 miles apart). One would assume that repeat DBE requests would again come to our institution for continued bleeding to attempt total enteroscopy through a combined approach. Thus, the low repeat DBE rate may indicate that patients did not have significant recurrent bleeding. Byeon *et al*[24] studied the diagnostic value of repeat DBE. Of 32 patients who underwent repeat DBE, all patients with negative initial DBE had a negative repeat DBE suggesting the reproducibility of the findings. On the other hand, seventeen of 21 patients with positive initial DBE again showed a probable bleeding source on repeat DBE[24]. Additionally, among the patients with normal findings at the first DBE procedure, 62.5% had no recurrent bleeding during the follow-up period of 40.4 ± 16.2 mo[25]. Negative DBE may portend a different clinical picture and a low likelihood of a small bowel source of bleeding.

DBE procedures are labor intensive, and can be tiring. The average examination time is approximately 60 to 90 min[9]. Our cases took longer than average to perform; however length of the procedure was not associated with diagnostic yield. It is known that colonoscopies have lower completion rates and adenoma detection rates in procedures performed in the afternoon compared with the morning, thought to be related to endoscopist fatigue. However, a study by Sanaka *et al*[26] evaluating DBE performance did not show a difference between morning or afternoon procedures. In our study we compared the cumulative effect of doing 2 or more procedures as opposed to one DBE a day. We found that there is an association with negative findings with more procedures in a day, which may indicate fatigue related factors affecting diagnostic and therapeutic yield. Thus, it may not be the timing of the procedure that matters but in fact the number of procedures one does given the long duration of DBE procedures.

There were several limitations to our study. First the small sample size and the retrospective design resulted in a wide confidence interval and less precise findings. Second of all, we were unable to accurately determine insertion depth and could not completely exclude the absence of findings in the unexamined small intestine as very few patients had complete enteroscopy.

In conclusion, this study may help stratify patients into high likelihood or low likelihood of negative diagnostic yield or therapy in DBE for gastrointestinal bleeding. This may help manage patients with multiple comorbidities and reduce health care costs by identifying those who are most likely to benefit from this time intensive procedure.

COMMENTS

Background

Double balloon endoscopy (DBE) is valuable in the setting of obscure gastrointestinal bleeding (OGIB). However, it is invasive, time-consuming and may be unable to identify a source for bleeding in 20% to 40% of OGIB cases.

Research frontiers

To identify patients' characteristics associated with DBE outcomes in investigation of OGIB.

Innovations and breakthroughs

To our knowledge, this is the first study to look at factors associated with both negative diagnostic and therapeutic yield of DBE. Fewer blood transfusion requirements, absence of arteriovenous malformations or ulcers on prior endoscopies and possibly endoscopist fatigue may predict a negative diagnostic and therapeutic yield of DBE.

Applications

This study may help stratify patients into high likelihood or low likelihood of negative diagnostic yield or therapy in DBE for gastrointestinal bleeding. This may help manage patients with multiple comorbidities and reduce health care costs by identifying those who are most likely to benefit from this time intensive procedure.

Peer review

This is a descriptive retrospective study into DBE. The results are therefore to be viewed with some caution and this in mind. Otherwise this study is worthy of publication.

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PROSPECTIVE STUDY

Efficacy and safety of endoscopic prophylactic treatment with undiluted cyanoacrylate for gastric varices

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Abstract

AIM: To evaluate the efficacy and safety of undiluted N-butyl-2 cyanoacrylate plus methacryloxysulfolane (NBCM) as a prophylactic treatment for gastric varices (GV) bleeding.

METHODS: This prospective study was conducted at a single tertiary-care teaching hospital between October 2009 and March 2013. Patients with portal hypertension (PH) and GV, with no active gastrointestinal bleeding, were enrolled in primary prophylactic treatment with NBCM injection without lipiodol dilution. Initial diagnosis of GV was based on endoscopy and confirmed with endosonography (EUS); the same procedure was used after treatment to confirm eradication of GV. After puncturing the GV with a regular injection needle, 1 mL of undiluted NBCM was injected intranasally into GV. The injection was repeated as necessary to achieve eradication or until a maximum total volume of 3 mL of NBCM had been injected. Patients were followed clinically and evaluated with endoscopy at 3, 6 and 12 mo. Later follow-ups were performed yearly. The main outcome measures were efficacy (GV eradication), safety (adverse events related to cyanoacrylate injection), recurrence, bleeding from GV and mortality related to GV treatment.

RESULTS: A total of 20 patients (15 male) with PH and GV were enrolled in the study and treated with undiluted NBCM injection. Only 2 (10%) patients had no esophageal varices (EV); 18 (90%) patients were treated with endoscopic band ligation to eradicate EV before inclusion in the study. The patients were followed clinically and endoscopically for a median of 31 mo (range: 6-40 mo). Eradication of GV was observed in all patients (13 patients were treated with 1 session and 7 patients with 2 sessions), with a maximum injected volume of 2 mL NBCM. One patient had GV recurrence, confirmed by EUS, at 6-mo follow-up, and another had late recurrence with GV bleeding after 35 mo of follow-up; overall, GV recurrence was observed in 2 patients (10%), after 6 and 35 mo of follow-up, and GV bleeding rate was 5% (1 patient). Mild epigastric pain was reported by 3 patients (15%). No mortality or major complications, including embolism, or damage to equipment were observed.

CONCLUSION: Endoscopic injection with NBCM, without lipiodol, may be a safe and effective treatment for primary prophylaxis of gastric variceal bleeding.

Key words: Gastric varices; Primary prevention; Endos-

copy; Gastrointestinal; Cyanoacrylates; Gastrointestinal hemorrhage

Core tip: In this prospective study, a total of 20 patients with portal hypertension and gastric varices (GV) were referred for primary prophylaxis of GV bleeding with endoscopic injection of N-butyl-2 cyanoacrylate plus methacryloxysulfolane (NBCM) without lipiodol dilution. Eradication of GV was observed in all patients. Overall, GV recurrence confirmed by endosonography was observed in 2 patients (10%), after 6 and 35 mo of follow-up. The prevalence of GV bleeding was 5% (1/20 patients). No major complications, such as embolism occurrence or death, were observed. Undiluted NBCM may be a safe and effective prophylactic against GV bleeding.

Franco MC, Gomes GF, Nakao FS, de Paulo GA, Ferrari Jr AP, Libera Jr ED. Efficacy and safety of endoscopic prophylactic treatment with undiluted cyanoacrylate for gastric varices. *World J Gastrointest Endosc* 2014; 6(6): 254-259 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i6/254.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i6.254

INTRODUCTION

Gastric varices (GV) are less common than esophageal varices (EV) and are estimated to be present in approximately 20% of patients with portal hypertension (PH). Risk of rupture is lower for GV than EV, however GV rupture can be extremely severe and difficult to control, and is associated with higher mortality than EV bleeding (25%-45%)[1].

Endoscopic ultrasound (EUS) is a very sensitive tool for GV detection[2]. It is also very useful for the assessment of GV obliteration with tissue adhesive injection and predicting recurrence of varices[3,4].

Since its introduction in the 1980s, endoscopic therapy with cyanoacrylate (CYA) improved the treatment of GV bleeding, achieving hemostasis rates of 89% to 100%, and reducing the rate of recurrent bleeding to below 30%[5,6]. Treatment of GV using glue injection is a well-established procedure. The most commonly used preparation of CYA is N-butyl-2 cyanoacrylate (Histoacryl®; B. Braun, Germany) diluted with lipiodol (Lipiodol Ultra Fluid®; Guerbert Roissy, France). The adverse events associated with CYA injection are usually minor (fever and mild abdominal pain); however, treatment can be associated with major and potentially life-threatening adverse events, usually related to peripheral embolization of polymerized glue, such as pulmonary embolism, splenic vein and portal vein thrombosis, splenic infarction and recurrent sepsis[7].

Glubran 2® (GEM; Viareggio, Italy) is a preparation of N-butyl-2 cyanoacrylate plus methacryloxysulfolane (NBCM). NBCM has a longer polymerization time than pure N-butyl-2 cyanoacrylate and does not usually require dilution with lipiodol[8]. NBCM seems to be as safe and effective as the combination of N-butyl-2 cyanoacrylate and lipiodol for GV obliteration[9].

Our study was conducted to evaluate the efficacy and safety of endoscopic injection of NBCM without lipiodol as a prophylactic treatment for GV bleeding.

MATERIALS AND METHODS

This prospective study was conducted between October 2009 and March 2013 at São Paulo Hospital, Federal University of São Paulo, Brazil, a tertiary-care teaching hospital. All patients gave written informed consent before enrollment. The study was approved by the Ethics Committee of our institution and was conducted in accordance with the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects.

The following outcomes were analyzed: efficacy (GV eradication); safety (adverse events related to cyanoacrylate injection); GV recurrence; GV bleeding and mortality related to GV treatment.

Patients

Patients with PH and large GV (> 10 mm) and no previous GV bleeding were eligible. Patients were followed clinically and endoscopically. Patient age varied from 18 to 75 years. Exclusion criteria were prior endoscopic treatment for GV, history of hepatocellular carcinoma, pregnancy.

Diagnosis of PH and liver disease was based on physical examination, biochemical tests, imaging studies including Doppler evaluation of the splenoportal axis and histological evidence. Patients were classified according to the Child-Pugh classification as having class A, B, or C liver disease.

Endoscopic diagnosis and interventions

All endoscopic procedures were performed under conscious sedation using the standard technique. Patients with esophageal varices who were high risk for bleeding underwent esophageal variceal eradication with endoscopic band ligation (EBL) prior to GV treatment. Sarin's classification[1] was used to classify GV as type 1 gastroesophageal varices (GOV-1), type 2 gastroesophageal varices (GOV-2), type 1 isolated gastric varices (IGV-1) or type 2 isolated gastric varices (IGV-2); Hashizume's schema[10] was used to classify the form of GV as tortuous (F1), nodular (F2) or tumorous (F3) and the presence of red color signs was recorded. Presence and severity of portal hypertensive gastropathy[11] were also documented. An EUS examination was performed to confirm the presence of GV.

GV puncture, preferentially at the center of the varix, was performed using a regular injection catheter (19 gauge needle), filled with distilled water. Once the intravariceal position of the needle was confirmed, 1 mL of undiluted NBCM was injected followed by enough

Table 1 Demographic characteristics of patients *n* (%)

Characteristics	Patients (*n* = 20)
Mean age in years	47.35 ± 11.37
Male	15 (75)
Etiology	
Viral	9 (45)
Alcohol	5 (25)
Schistosomiasis	2 (10)
Other	4 (20)
Child-Pugh class	
A	13 (65)
B	7 (35)
Prior history of UGB	10 (50)
Eradication of EV	18 (90)
Propranolol use	12 (60)

UGB: Upper gastrointestinal bleeding; EV: Esophageal varices.

Table 2 Endoscopic characteristics of patients *n* (%)

Characteristics	Patients (*n* = 20)
GV Classification	
GOV1	13 (65)
GOV2	3 (15)
IGV1	4 (20)
Form of GV	
F1	7 (35)
F2 or F3	13 (65)
PHG	
Mild	16 (80)
Severe	4 (20)
RCS	4 (20)

GV: Gastric varices; GOV1: Type 1 gastroesophageal varices; GOV2: Type 2 gastroesophageal varices; IGV1: Type 1 isolated gastric varices; PHG: Portal hypertensive gastropathy; RCS: Red color signs.

distilled water to flush all the glue into the GV. The needle was then removed. If necessary, glue injection was repeated at a subsequent session (at 3 mo), up to a maximum injected volume of 2 mL of NBCM.

GV eradication was assessed by endoscopically detectable features, no varices, residual scar or residual hard varices - assessed by touching with closed forceps - and EUS was used to confirm that there was no blood flow into residual varices. A linear array echoendoscope (EG-530 UT; Fujinon, Saitama, Japan) with VP4400 processor (Fujinon; Saitama, Japan) or SU-7000 ultrasonic processor (Fujinon; Saitama, Japan) was used to perform EUS. Endoscopic follow-up was performed at 3-mo intervals until GV eradication was observed; subsequent reevaluations were made at 3, 6 and 12 mo. Later follow-ups were performed yearly. Any clinical suspicion of gastrointestinal bleeding prompted an endoscopic examination.

Statistical analysis

Quantitative variables were expressed as means ± SD or medians (ranges). Qualitative variables were expressed as frequencies and percentages. Statistical analysis was performed using SPSS 13.0 for Windows.

RESULTS

A total of 20 patients with PH and large GV were included in this study. Demographic characteristics of patients are listed in Table 1. According to the Child-Pugh classification 13 (65%) patients had class A disease, and 7 (35%) class B. We attributed the higher than normal proportion of patients with Child-Pugh A to the design of the study, which selected patients for primary prophylaxis of GV bleeding. Ten patients had a history of upper gastrointestinal bleeding (UGB), due to EV bleeding. Eighteen (90%) patients underwent endoscopic treatment with EBL to eradicate EV before the beginning of the study; the remaining patients had no EV. Twelve patients were taking Propranolol. Most patients presented with GV type GOV1. The endoscopic characteristics of patients are listed in Table 2.

Table 3 Overall results of gastric varices treatment with cyanoacrylate injection *n* (%)

Characteristics	Patients (*n* = 20)
GV eradication	20 (100)
Number of sessions	
1	13 (65)
2	7 (35)
Mean volume NBCM injected in mL	1.37 ± 0.48
Recurrence rate	
3 mo	0
6 mo	1 (5)
> 2 yr	1 (5)
Total	2 (10)
Median follow-up in months (range)	31 (6-40)
Late bleeding rate	1 (5)
Minor adverse events[1]	3 (15)
Major adverse events	0
Overall mortality rate	0

[1]Epigastric pain. GV: Gastric varices; NBCM: N-butyl-2 cyanoacrylate plus methacryloxysulfolane.

After treatment with undiluted NBCM GV eradication was observed in all patients (Table 3). GV obliteration was achieved in 1 session in 13 (65%) patients and in 2 sessions in 7 (35%) patients, with a mean NBCM volume of 1.37 mL (SD = ± 0.48) (Figure 1). Eighteen patients underwent EUS before CYA injection and GV was confirmed in all patients; 12 (66%) had perigastric collaterals, 9 (50%) had paragastric collaterals and 5 (28%) had perforating veins. Eradication of GV after treatment was confirmed in 18 patients using EUS. In two patients GV eradication was based on endoscopic criteria, without EUS evaluation. Only 1 (5%) patient experienced GV recurrence, confirmed by EUS, at 6-mo follow-up. He had hepatitis C infection (Child-Pugh A), and large (F2) type 2 gastroesophageal varices with red spots.

A late endoscopic follow-up, at least 2 years after eradication, was performed in 16 (80%) patients. Late recurrence of GV, confirmed by EUS, was observed in one patient at a 35-mo follow-up. This patient had alcohol-

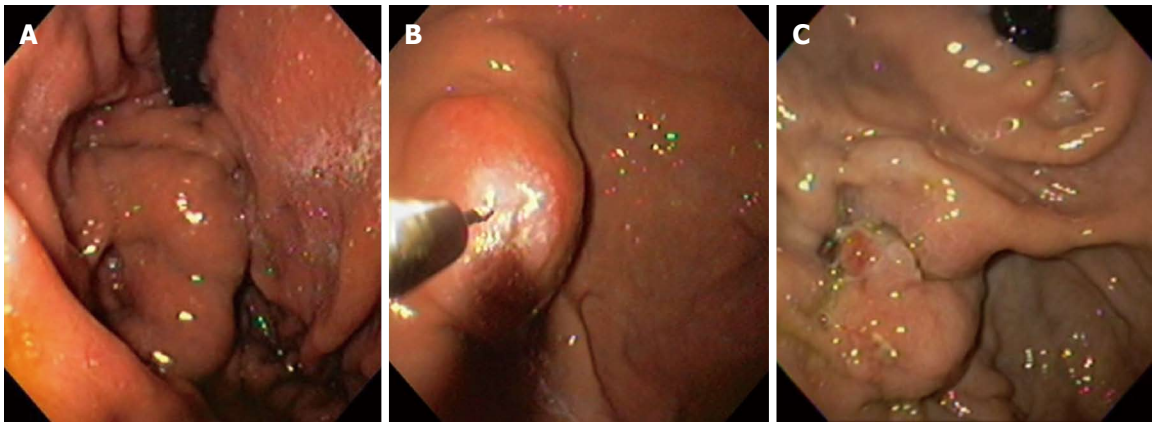

Figure 1 Endoscopic view of cyanoacrylate injection therapy. A: Initial view before injection; B: Aspect immediately after glue injection; C: Six months after injection.

related liver disease (Child-Pugh B), large (F2) type 1 gastroesophageal varices at the first endoscopic evaluation. He presented with upper gastrointestinal bleeding with no significant clinical consequences, and was treated with a second CYA injection and suffered no adverse events. Four patients were lost during follow-up, although none were readmitted to our hospital with GV bleeding. Overall, the GV recurrence rate was 10% and the GV bleeding rate was 5%, over a median of 31 mo (range: 6-40 mo).

No mortality was observed during our study. Mild epigastric pain was reported by 3 patients (15%). No major adverse events (systemic embolism, sepsis or gastrointestinal bleeding due CYA injection) or damage to equipment were observed (Table 3).

DISCUSSION

Endoscopic therapies for esophageal varices, such as band ligation and injection of sclerosant agents, have also been used to treat GV bleeding. However the results in terms of hemostasis, rebleeding and GV obliteration are poor compared with CYA injection[5,12], so endoscopic CYA injection has been recommended as an initial treatment for acute GV bleeding in recent consensus and guidelines[13-15]. Treatment of GV bleeding using transjugular intrahepatic portosystemic shunt (TIPS) has also been studied; although TIPS is as safe and clinically effective as CYA injection, TIPS placement is associated with higher long-term morbidity, due to increased incidence of encephalopathy, and it is also more expensive[16].

There have been recent reports of increased survival with primary and secondary prophylaxis of GV bleeding with CYA injection[17,18], but only a few studies have evaluated the safety and long-term efficacy of prophylactic CYA injection[19,20]. In this study, prophylactic GV eradication was achieved in all patients with NBCM injection. The GV recurrence rate was 10% (2/20) and the prevalence of late GV bleeding was 5% (1/20). There were no reported deaths related to GV bleeding during follow-up. These results are similar to previously published reports on prophylactic treatment of GV with Histoacryl® plus lipiodol over follow-up periods of up to 2 years. Previous studies reported eradication rates ranging from 95% to 100%; GV recurrence rates ranging from 4.3% to 14.0%; GV rebleeding rates from 4.3% to 8.0% and GV-associated mortality rates up to 4.3%[19,20].

Greater dilution of CYA with lipiodol seems to increase the risk of embolization[21]. Most reported major adverse events after CYA injection, such as distal embolization and death, occurred in patients in whom this combination was used[7,21,22].

Dhiman *et al*[23] reported no embolic events after switching from CYA diluted with lipiodol (1:1) to undiluted CYA injection as a treatment for GV bleeding. Similarly Kumar *et al*[24] reported no clinically significant embolization in 87 patients treated for GV bleeding using 261 injections of undiluted CYA.

NBCM (Glubran 2®) does not require dilution with lipiodol because it polymerizes a little more slowly than pure N-butyl-2 cyanoacrylate (Histoacryl®)[8]. One may hypothesize that after injection into the varix NBCM in contact with blood polymerizes faster than N-butyl-2 cyanoacrylate diluted with lipiodol. Such fast local intravasal polymerization of undiluted NBCM might be associated with reduced incidence of embolic events. Further research is required to investigate this hypothesis as there is currently no published empirical evidence.

In our study there were no major adverse events over 27 injections of undiluted NBCM in 20 patients for GV prophylactic eradication. Saracco *et al*[25] reported a single fatal systemic embolism after treatment of GV bleeding with undiluted NBCM using 2 mL of NBCM in one session, in a patient with idiopathic PH. It is recommended that CYA be used as 1 mL injections per session, because larger injected volumes are associated with a higher risk of peripheral embolization[26].

We used EUS to assess GV obliteration and recurrence after treatment with NBCM injections. Flow in residual GV, which would indicate that further CYA injection were required[27], can be detected using EUS. EUS has also been used to support GV eradication by CYA injection into gastric perforating veins, a method which

appears to be safe and effective, with a low recurrent bleeding rate[28].

This study is significant because there are only few reports on the efficacy and long-term safety of prophylactic CYA injection for GV[19,20]. Furthermore, this study is the first to have evaluated the feasibility, efficacy and long-term safety of NBCM as a prophylactic treatment for GV bleeding in adults.

In conclusion, although our findings are subject to some limitations (small series, patients with good liver function, one arm design in a single institution, and loss to follow up of some patients), our results suggest that endoscopic injection with NBCM, without lipiodol, may be a safe and effective primary prophylactic for gastric variceal bleeding.

COMMENTS

Background

Endoscopic cyanoacrylate (CYA) injection has been recommended as initial treatment for gastric varices (GV) acute bleeding. Band ligation and injection of sclerosant agents produce worse outcomes in terms of GV hemostasis and rebleeding than CYA injection. TIPS is associated with increased incidence of encephalopathy.

Research frontiers

Although a recent publication of Mishra *et al* has reported reduced risk of first bleeding and lower mortality with CYN injection, compared with beta-blockers, for prophylactic treatment of large GV, only a few studies have evaluated the safety and long-term efficacy of prophylactic CYA injection.

Innovations and breakthroughs

N-butyl-2 cyanoacrylate diluted with lipiodol is the most commonly used CYA preparation used for endoscopic injection into GV, however it is associated with a risk of peripheral embolization of polymerized glue. N-butyl-2 cyanoacrylate plus methacryloxysulfolane (NBCM) does not usually require dilution with lipiodol for GV injection, and may be associated with a lower incidence of adverse events. This is the first study to have evaluated the feasibility, efficacy and long-term safety of NBCM as a prophylactic treatment for GV bleeding in adults.

Applications

Endoscopic treatment with CYN injection is low cost, widely available, and not hard to do.

Terminology

NBCM is a preparation of N-butyl-2 cyanoacrylate with methacryloxysulfolane. NBCM has a longer polymerization time than pure N-butyl-2 cyanoacrylate.

Peer review

It is interesting that this study was the first to determine the efficacy and safety of prophylactic treatment by undiluted N-butyl-2 Cyanoacrylate plus Methacryloxysulfolane (NBCM) for gastric varices. And the authors concluded endoscopic injection with NBCM, without lipiodol, may be a safe and effective treatment for primary prophylaxis of gastric varices bleeding.

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CASE REPORT

Endoscopic treatment of duodenal fistula after incomplete closure of ERCP-related duodenal perforation

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Author contributions: Yu DW and Hong MY treated the patient and collected the patient's clinical data; Hong SG supervised the two doctors, designed and wrote the case report.

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) is an important diagnostic and therapeutic modality for various pancreatic and biliary diseases. The most common ERCP-induced complication is pancreatitis, whereas hemorrhage, cholangitis, and perforation occur less frequently. Early recognition and prompt treatment of these complications may minimize the morbidity and mortality. One of the most serious complications is perforation. Although the incidence of duodenal perforation after ERCP has decreased to < 1.0%, severe cases still require prolonged hospitalization and urgent surgical intervention, potentially leading to permanent disability or mortality. Surgery remains the mainstay treatment for perforations of the luminal organs of the gastrointestinal tract. However, evidence from case reports and case series support a beneficial role of endoscopic clipping in the closure of these defects. Duodenal fistulas are usually a result of sphincterotomies, perforated duodenal ulcers, or gastrectomy. Other causative factors include Crohn's disease, trauma, pancreatitis, and cancer. The majority of duodenal fistulas heal with nonoperative management. Those that fail to heal are best treated with gastrojejunostomy. Recently proposed endoscopic approaches for managing gastrointestinal leaks caused by fistulas include fibrin glue injection and positioning of endoclips. Our patient developed a secondary persistent duodenal fistula as a result of previous incomplete closure of duodenal perforation with hemoclips and an endoloop. The fistula was successfully repaired by additional clipping and fibrin glue injection.

Key words: Perforation; Duodenal; Endoscopic retrograde cholangiopancreatography; Fistula; Glue

Core tip: In this report, a patient developed a secondary persistent duodenal fistula following an incomplete endoscopic closure of endoscopic retrograde cholangiopancreatography-related duodenal perforation with hemoclips and an endoloop. The fistula was successfully managed by further endoscopic treatment with additional clipping and fibrin glue injection. This case emphasizes that endoscopists should remain aware of the possibility for a secondary persistent fistula formation due to incomplete closure when long-standing fluctuating free air is detected after endoscopic treatment of bowel perforation.

Yu DW, Hong MY, Hong SG. Endoscopic treatment of duodenal fistula after incomplete closure of ERCP-related duodenal perforation. *World J Gastrointest Endosc* 2014; 6(6): 260-265 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i6/260.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i6.260

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP), an important technique used for diagnosis and therapeutic modality of various pancreatic and biliary diseases, is plagued by serious complications that can

lead to significant morbidity. Overall, complications occur in 5%-10% of cases following ERCP with or without sphincterotomy[1]. The incidences of post-ERCP pancreatitis, hemorrhage, cholangitis, and perforation are 3.5%-3.8%, 0.9%-1.3%, 1.0%-5.0%, and 0.1%-1.1%, respectively. The overall mortality rate after ERCP is 0.3%[2,3]. Early recognition and prompt treatment of these complications may minimize the morbidity and mortality. One of the most feared complications is perforation. Perforation management depends on the location, radiologic imaging findings, and severity of the injury. The majority of duodenal fistulas are surgical complications caused by inadequate closure or devascularization of the duodenum. Other causative factors include Crohn's disease, trauma, peptic ulcer disease, pancreatitis, and cancer[4]. The treatment of choice for patients with duodenal perforation is primary surgical closure. There have been reported cases of endoscopic closures of ERCP-related duodenal perforations using hemoclips[5]. Despite various strategies, from a minimally invasive approach with nutritional support to a more risky open surgery, duodenal fistulas remain difficult to treat[6].

To the best of our knowledge, there has been only one previously published report on a secondary duodenal fistula after ERCP-related duodenal perforation[7]. Recently, a patient in our care experienced a case of duodenal perforation following ERCP. Despite immediate application of multiple hemoclips and an endoloop to close the defect, a secondary persistent duodenal fistula, communicating with the peritoneal cavity, developed due to incomplete primary endoscopic closure. The fistula was successfully treated by further endoscopic treatment with additional clipping and fibrin glue injection.

CASE REPORT

A 66-year-old woman was admitted to our emergency department complaining of upper abdominal pain and vomiting, which occurred 3 h prior to her admission. On physical examination, her blood pressure was 130/75 mmHg, heart rate was 93 beats/min, and body temperature was 36.8 ℃. Palpation revealed tenderness in the right upper quadrant of the abdomen. Laboratory test results were as follows: hemoglobin concentration, 11.5 g/dL; white blood cell count, 6800 cells/μL; aspartate aminotransferase, 222 IU/L; alanine aminotransferase, 86 IU/L; total bilirubin, 0.6 mg/dL; alkaline phosphatase, 49 IU/L; and gamma-glutamyl transpeptidase, 52 IU/L.

On the initial abdominal computed tomography (CT), a small (approximately 4 mm) distal common bile duct (CBD) stone was suspected. ERCP was performed on the day of admission (Figure 1A). While placing the scope in a short scope position, the scope was rapidly withdrawn into the pylorus and an approximately 10 mm linear perforation occurred in the lateral wall of the duodenal bulb. Multiple hemoclips (Olympus Corp., Tokyo, Japan) with a detachable plastic snare (Endoloop; Olympus Corp.) were immediately applied to close the perforation (Figure 1B-D). The patient developed chills and diffuse abdominal pain; the chest X-ray showed free air under both hemidiaphragms (Figure 2). Following ERCP, laboratory test results were as follows: hemoglobin concentration, 10.7 g/dL white blood cell count, 7900 cells/μL; aspartate aminotransferase, 485 IU/L; alanine aminotransferase, 438 IU/L; total bilirubin, 0.9 mg/dL; alkaline phosphatase, 59 IU/L; C-reactive protein (CRP), 81 mg/L; amylase, 32 IU/L; and lipase 25.7 IU/L. Nil per os was initiated with peripheral parenteral nutrition, intravenous broad spectrum antibiotic administration, and nasogastric tube drainage.

Abdominal pain was relieved on the sixth day after the endoscopic treatment, and the amount of free air under both hemidiaphragms was decreased on the chest X-ray. The laboratory test results showed that liver function was normalized and the CRP level decreased to 32.3 mg/L. The patient remained symptom-free for 3 d, and was permitted to take sips of water on the ninth day after duodenal perforation. Although the serum CRP level did not increase, the chest X-ray showed increased free air under both hemidiaphragms two days later. A follow-up CT scan with oral contrast (Gastrografin) showed no contrast leakage, however, it did show moderate amount of pneumoperitoneum (Figure 3). To determine if surgery was needed, a surgeon was consulted and the decision was made to continue conservative management for one more week. Although the patient remained symptom-free during this one-week period, the second follow-up CT showed a small fistula, approximately 2 mm in diameter, communicating with the peritoneal cavity at the prior perforation site in the duodenum (Figure 4). The previous CBD stone was not observed, and we presumed the stone had passed spontaneously. The serum CRP level was nearly normalized. With patient and medical guardian's consent, a decision was made to perform endoscopic treatment before the operation. The secondary duodenal fistula was successfully closed using endoscopic treatment with additional clipping and fibrin glue (Greenplast®) injection (Figure 5). The free air under both hemidiaphragms significantly decreased the day after the endoscopic treatment, and the patient resumed a scheduled diet followed by a discharge three weeks after the development of duodenal perforation.

DISCUSSION

Although ERCP-related perforation is reported in less than 1% of cases, mostly due to sphincterotomy, perforation needs to be diagnosed immediately and treated promptly. Delays in the diagnosis and intervention of the perforation may lead to the development of sepsis and multiorgan failure, resulting in high mortality (8%-23%)[8-10]. The most commonly used classification of ERCP-induced perforations, suggested by Stapfer *et al*[11], is based on the mechanism of perforation and forecasts the need for surgery depending on the anatomic location and severity of injury. Another classification proposed

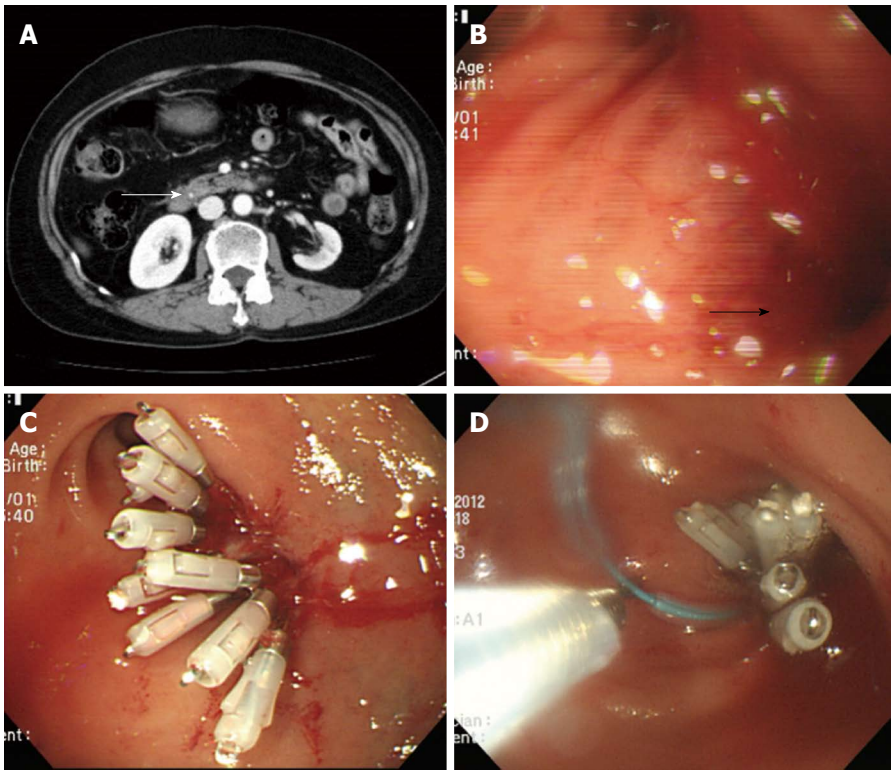

Figure 1 Initial abdominal computed tomography and endoscopic findings during endoscopic retrograde cholangiopancreatography. A: Computed tomography showed a small common bile duct stone (thin white arrow); B: During endoscopic retrograde cholangiopancreatography, a 10 mm-sized perforation developed in the lateral wall of the duodenal bulb during inadvertent rapid withdrawal of the duodenoscope (thick black arrow); C and D: Multiple hemoclips and an endoloop were immediately applied for the defect closure.

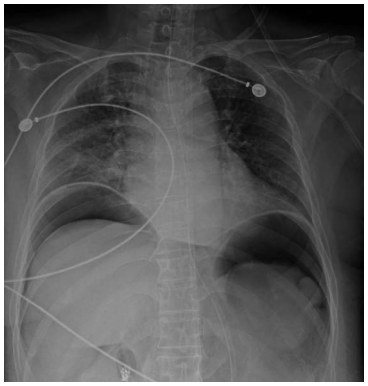

Figure 2 Chest X-ray after endoscopic retrograde cholangiopancreatography. The scan shows a large amount of pneumoperitoneum below both the hemidiaphragms.

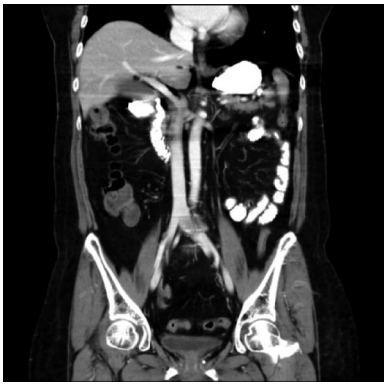

Figure 3 Follow-up abdominal computed tomography after duodenal perforation. No contrast leakage was detected into the peritoneum at the periduodenal lesion after endoscopic treatment; however, a moderate amount of pneumoperitoneum was present.

by Howard *et al*[12] categorizes ERCP-induced perforation into three types: guidewire, periampullary, and duodenal perforation.

The treatment of post-ERCP perforation should be determined based on the type, the severity of the leak, and clinical manifestations. In our case, the perforation was classified as type I using Stapfer's classification. Type I injury is caused by the endoscopic tip or insertion tube resulting in a large perforation requiring immediate surgery. However, if immediate treatment by endoscopic technique is not possible, conservative management with close monitoring may be a better option[9-11]. Sphincterotomy-related, guide-wire-related, or stent-related perforations can be treated by the endoscopic method with adequate ductal drainage above the perforation site[9,11]. In previous case reports, ERCP-related duodenal perforations were managed successfully with the use of endoclips[5,13]. However, adequate closure required inclusion of the bowel wall submucosal layer, which clips cannot reliably ensure. The patients need to be carefully selected, since the method is applicable to small, early detected,

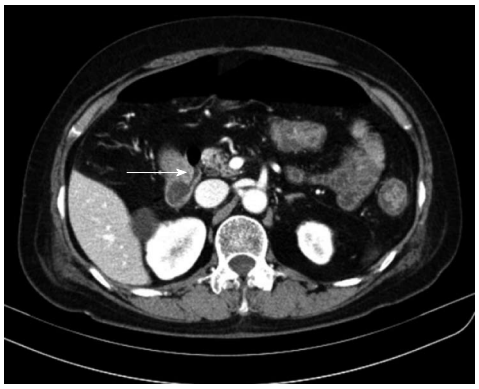

Figure 4 Second follow-up abdominal computed tomography after duodenal perforation. The scan shows a small fistula communicating with the peritoneal space, at the previous perforation site in the duodenal bulb (arrow), and absence of a common bile duct stone.

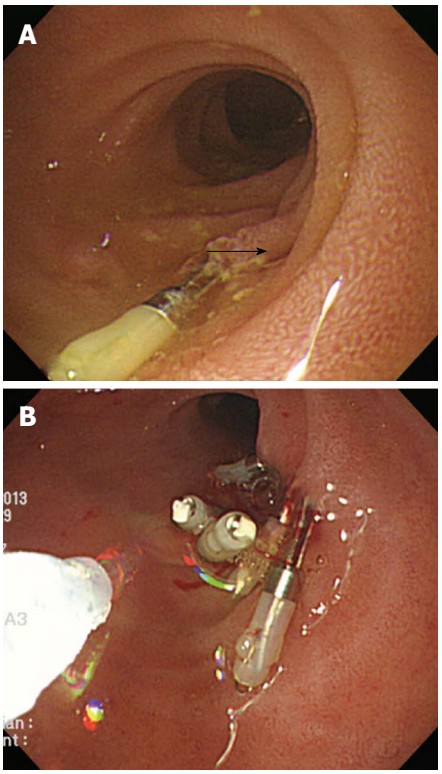

Figure 5 Endoscopic findings of the second endoscopic closure. A: A suspicious fistulous opening was detected at the previous perforation site (arrow); B: An application of additional multiple hemoclips and fibrin glue injection was successfully performed at the site of the suspicious fistulous opening.

and well-defined perforations, which meet all the criteria for conservative management such as the absence of abdominal signs and fluid collections.

Our patient was immediately treated with endoscopy using multiple hemoclips and fibrin glue injection despite the perforation being relatively large (approximately 10 mm) for endoscopic closure. Although the endoscopy went well, a persistent secondary duodenal fistula, communicating with the peritoneal cavity, was observed on repeat CTs. Furthermore, free air was detected under the hemidiaphragms, despite the lack of extravasation of the contrast and the typical abdominal pain associated with the condition. An explanation for the free air is that it leaked from the fistula.

Gastrointestinal fistulas that result from surgery, disease, or trauma, are first treated medically. This includes parenteral nutrition and bowel rest, as well as control of infection, correction of electrolyte imbalance, and local care of the fistula tract. Patients with obstruction of the intestinal lumen downstream of the fistula or patients who have a persistent fistula, which fails to close after prolonged medical treatment, require surgical treatment[4,6]. Recently, various endoscopic approaches have been proposed for managing gastrointestinal leaks caused by fistulas, including fibrin glue injection, endoclip positioning, suturing devices, stent insertion, and endoluminal vacuum devices[14-16].

Fibrin glue, a formulation made up of glue and thrombin, is applied by a double injector system to repair tears. Mixing of these two components results in a fibrin coagulum formation with a short onset time. Fibrin injection can be used for sealing only very small leaks (< 5 mm diameter) not connected to the cavities, and in the absence of abscesses[17]. In a retrospective analysis of 52 patients with fistulas and anastomotic leakages in the gastrointestinal tract, endoscopic treatment was successful in 56% of cases. The success rate for fibrin glue application as the sole endoscopic therapy was 37%[16]. In short, endoscopic treatment with fibrin glue should be considered as a valuable option for treating fistula and anastomotic leakage of the gastrointestinal tract.

Standard clips are widely used in endoscopy for mechanical hemostasis following post-procedural bleeding. The importance of their role in endoscopic closure of small perforations, immediately following polypectomy or mucosectomy, is widely recognized. However, data on the endoclip efficacy in treating post-surgical leaks and fistulas are variable. Furthermore, the low closure strength of endoclips limits their use in scarred and hardened post-surgical tissues. To overcome this limitation, a new over-the-scope clip system (OTSC; Ovesco Endoscopy AG, Tubingen, Germany), consisting of a large nitinol clip loaded on the tip of the endoscope, has recently been developed. This device enables capturing of a large amount of tissue, powerfully compressing and approximating the margins of a lesion, thus favoring its healing[14,18].

CBD stones, especially the small ones, may pass spontaneously in a significant number of patients[19,20]. The absence of a stone in the patient's CBD on follow-up CT could be explained by its spontaneous passage. Contrast leakage was not observed at the previous perforation site after endoscopic closure on the second follow-up CT. However, the leakage of air into the peritoneal space could have occurred through the secondary small fistula due to prior inadequate closure. Consequently, delayed formation of a secondary fistula should be considered in the presence of long-term, fluctuating free air under the diaphragm, viewed on abdominal imaging, following the

endoscopic treatment.

In summary, despite the initial endoscopy treatment with hemoclips and an endoloop, a secondary persistent duodenal fistula developed due to incomplete previous endoscopic closure of the duodenal perforation after ERCP. Additional clipping and fibrin glue injections were successful in closing of the fistula.

COMMENTS

Case characteristics

Diffuse abdominal discomfort after endoscopic closure of the endoscopic retrograde cholangiopancreatography (ERCP)-related perforation with no specific symptom six days after ERCP.

Clinical diagnosis

Failure or inadequacy of endoscopic treatment for ERCP-related duodenal perforation.

Differential diagnosis

Residual common bile duct stone or periduodenal abscess formation at the perforation site was possible.

Laboratory diagnosis

C-reactive protein was elevated after ERCP-related perforation followed by a decrease six days after endoscopic treatment.

Imaging diagnosis

A secondary duodenal fistula formation into the peritoneal cavity on abdominal computed tomography (CT) due to inadequate primary endoscopic treatment for ERCP-related perforation.

Treatment

After failed endoscopic closure of the ERCP-related duodenal perforation and the secondary fistula formation at the perforation site on abdominal CT 16 d after ERCP, a rescue endoscopic treatment with hemoclips and fibrin glue was successfully achieved, and persistent free air on chest X-ray disappeared a day after the rescue treatment.

Related reports

The retroperitoneal duodenal perforation after biliary sphincterotomy led to development of the secondary duodenal fistula, refractory to laparotomy and drainage with conservative treatment, which was successfully managed with biliary self-expandable metallic stent insertion.

Term explanation

Fibrin glue, a biologic tissue adhesive, is made up of fibrinogen and thrombin, and has been used endoscopically for the treatment of bleeding, fistulas, and anastomotic leak.

Experiences and lessons

Clinicians should consider the possibility of a secondary fistula formation into the peritoneal cavity, due to the presence of persistent fluctuating free air on chest X-ray after endoscopic treatment of a bowel perforation.

Peer review

A very clear and concise case presentation. Well-structured and correctly documented. It is an interesting experience and we appreciate for sharing it with the readers.

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EDITORIAL

Management of early asymptomatic gastrointestinal stromal tumors of the stomach

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Abstract

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the digestive tract. Approximately two thirds of clinically manifest tumors occur in the stomach, nearly one third in the small bowel, and the rest in the colorectal region with a few cases in the esophagus. GIST originate within the smooth muscle layer in the wall of the tubular gastrointestinal tract and grow mostly toward the serosa, far less often toward the mucosa. In the latter case, ulceration may develop and can cause gastrointestinal bleeding as the cardinal symptom. However, most GIST of the stomach are asymptomatic. They are increasingly detected incidentally as small intramural or submucosal tumors during endoscopy and particularly during endoscopic ultrasound. Epidemiological and molecular genetic findings suggest that early asymptomatic GIST of the stomach (< 1 cm) show self-limiting tumorigenesis. Thus, early (< 1 cm) asymptomatic gastric GIST (synonym: micro-GIST) are found in 20%-30% of the elderly. The mostly elderly people with early gastric GIST have an excellent GIST-specific prognosis. Patients with early GIST of the stomach can therefore be managed by endoscopic surveillance.

Key words: Mirco-gastrointestinal stromal tumors; Gastrointestinal stromal tumor; Gastric; Neoplasia; Cancer; Endoscopy; Endoscopic ultrasound

Core tip: Small gastric gastrointestinal stromal tumors (GIST) are by far the commonest neoplasias of the stomach. Thus, early gastric GIST of less than 1 cm in size are found in 20%-30% of the elderly. The natural disease-specific prognosis of early gastric GIST (< 1 cm), also called micro-GIST, is excellent in the mostly elderly patients. Micro-GIST of the stomach appear to have a self-limiting tumorigenesis. Local endoscopic or surgical resection of early asymptomatic GIST (< 1 cm) of the stomach is in general not indicated in the elderly. Instead endoscopic surveillance is advised.

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INTRODUCTION

Gastrointestinal stromal tumors (GIST) originate from mesenchymal cells, *i.e.*, the socalled interstitial cells of Cajal that act as pacemakers, or from a common precursor cell along the intestine. Approximately 50%-70% of clinically manifest tumors arise in the stomach, 20%-30% in the small bowel, 5%-15% in the large bowel and less than 5% in the esophagus or other locations. The mean age

at diagnosis is between 66 and 69 years for both women and men. About 3% of clinically manifest GIST are diagnosed before the age of 21 years. Their occurrence is predominantly sporadic[1]. There may be a connection with hereditary diseases in a small percentage of cases (neurofibromatosis type 1, Carney triad, familial GIST and mastocytosis).

Clinically manifest GIST are rare with an annual incidence rate of 10 to 20 cases per million population[2]. Much more common, on the other hand, are early (up to 1 cm large) asymptomatic gastric GIST, also called micro-GIST, which are found in 20%-30% of the elderly[3-5]. The striking discrepancy between the incidence of GIST in autopsy stomachs or gastrectomy specimens and the incidence of clinically manifest GIST suggests that early asymptomatic GIST of the stomach are precursor lesions from which clinically manifest GIST arise only in exceptional cases. Thus the characteristics of early asymptomatic GIST of the stomach will be discussed here with reference to clinical management.

SYMPTOMS AND DIAGNOSIS

The vast majority of early gastric GIST are asymptomatic. Patients with symptomatic gastric GIST, which are usually larger than 2-3 cm, most commonly present with gastrointestinal bleeding, anemia, epigastric pain and sometimes palpable resistance, vomiting, and weight loss.

GIST metastasize mainly to the liver and peritoneum. Lung and bone metastases are unusual, and lymph node metastases are rare. Laboratory examinations are of no diagnostic value. Metastases can be detected by ultrasound and CT scans; the latter may be optionally combined with positron emission tomography (FDGPET/CT)[6].

ENDOSCOPY

Gastroscopy is the standard procedure for diagnosing GIST of the stomach. Endoscopy detects the mostly intramural tumors and also enables endoscopic ultrasound (EUS)-guided acquisition of cytological and histological samples. The latter is imperative for a definitive diagnosis. In contrast to histology, cytology does not allow for determination of the mitotic rate. In emergency situations where urgent surgery is indicated, the clinically suspected diagnosis of GIST is verified postoperatively by histological evaluation of the resected tumor specimen.

Typical endoscopic findings in patients with early gastric GIST are shown in Figure 1. Early asymptomatic GISTs of the stomach are mostly detected incidentally during gastroscopy as submucosal protrusions < 1 cm in diameter. Due to their submucosal or intramural location, however, they usually cannot be verified histologically by routine biopsies of the superficial normal mucosa. Endoscopic submucosal resection (ESMR) might be a procedure for diagnosing the very few, early gastric GIST that are confined to the mucosa and submucosa[7]. No reports are available on ESMR or endoscopic mucosal resection (EMR) for early gastric GIST[8]. R0 resection of the more common gastric GIST that arise from the muscularis propria cannot be achieved using traditional endoscopic techniques. However, a lot of them can be completely en bloc resected by endoscopic submucosal dissection in expert hands[9]. (Laparoscopic) Surgical resection is the method of choice for larger GIST.

EUS AND EUS-FNA

EUS plays a decisive role in the diagnosis, the measurement of size, the assessment of local infiltration, and clinical management of submucosal or intramural lesions of the stomach. It reliably distinguishes mucosal lesions from a submucosal mass or extramural compression. EUS is often able to correctly identify the type of lesion based on its echo features, its assignment to a specific wall layer or its location outside the stomach.

EUS examinations can be performed with a radial scanner (360°) or a linear echoendoscope. Filling the stomach with water optimizes acoustic coupling of the probe to the stomach wall. Gastric GIST typically arise from the fourth echo layer of the stomach wall (muscularis propria), rarely also from the submucosa (third echo layer). They are usually visualized as oval-to-elliptical hypoechoic lesions with a smooth border. Large GIST often show a large central anechoic blood vessel or hyperechoic air bubbles in the case of central ulceration. On EUS images, large GIST can appear inhomogeneous with hypo- and hyperechoic parts. GIST characteristically lack paragastric lymph node metastases; this too can be clearly demonstrated with EUS.

In the acquisition of cytological and histological samples, EUS-guided biopsy of the submucosal or intramural GIST plays a decisive role. The definitive cytological and/or histological verification of larger gastric GIST is currently achieved in 50%-70% of EUS-guided fine-needle aspiration (FNA) or EUS-guided Trucut punch biopsies[10-15]. The histological diagnosis of GIST requires immunohistochemical detection of CD117 and particularly in CD117-negative tumors of DOG1 with the corresponding histomorphological findings. Most early GIST of the stomach can be followed-up by endoscopic examinations (EUS) even without initial histological confirmation.

PATHOLOGY, METASTATIC RISK AND PROGNOSIS

The diagnosis of GIST first came into existence in 1998 when the CD117 antigen was identified as being almost invariably expressed by GIST in over 90% of the cases; in contrast, leiomyomas, leiomyosarcomas and other spindle-cell gastrointestinal tumors are typically CD117-negative. CD117 antigen is the type Ⅲ transmembrane receptor tyrosine kinase KIT, a KIT proto-oncogene product[1]. Approximately 95% of GIST in adulthood

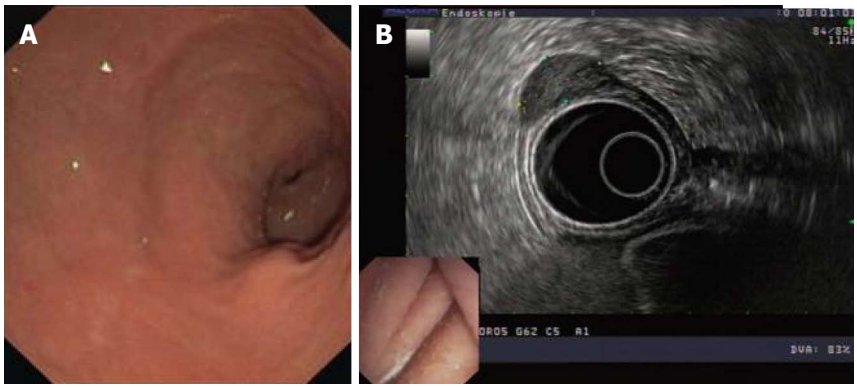

Figure 1 Typical endoscopic features of an early gastrointestinal stromal tumors of the stomach. A: Endoscopic image of an early GIST of the stomach; B: Endosonographic image of an early GIST of the stomach. Modified from reference [33]. GIST: Gastrointestinal stromal tumors.

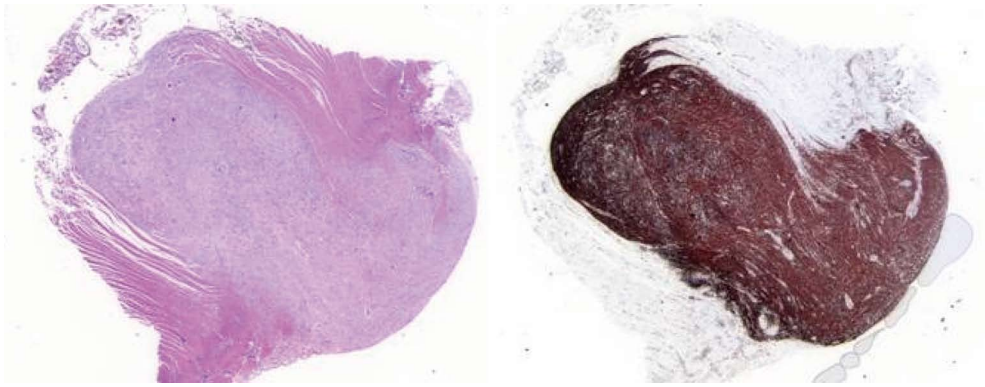

Figure 2 Histological images of an early gastrointestinal stromal tumors of the stomach. A: Gastric GIST of the muscularis propria displaying spindle cell type (HE stain); 2B: GIST of the muscularis propria displaying spindle cell type (CD 34 stain). Modified from reference [33]. GIST: Gastrointestinal stromal tumors.

overexpress KIT. Nearly 80% of GIST show *KIT* gene mutations that lead to constitutive activation of the KIT receptor. More than 60% of the *KIT* activating mutations occur in exon 11. About 10% of the cases have mutations in exon 9, much more rarely (< 2%) in exon 13 or 17. Instead of *KIT* mutations, about 15% of all GIST have analogous mutations in the plateletderived growth factor receptor alpha (*PDGFRA*) gene; here they cluster in exon 18, more rarely in exon 12 or 14. They are preferentially detected in the stomach but hardly ever in other gastrointestinal locations. The tumors often show an epithelioid histomorphological phenotype[16,17].

Much attention is nowadays payed to the diagnostic marker DOG1, a protein with 8 transmembrane domains that constitutes a calcium-regulated chloride ion channel. DOG1 probably has even higher sensitivity for GIST than CD117. Moreover, the marker shows high sensitivity for CD117-negative GIST[18,19]. In non-GIST, on the other hand, DOG1 positivity has only been observed in a few isolated cases. GIST express CD34 in 70%-80% of the cases, whereas a KIT expression is found in more than 90% of cases. Immunohistochemical stains for CD117, DOG1 and CD34 are now routinely used in the identification and diagnosis of GIST (Figure 2). Antibodies against smooth muscle actin, desmin and S100 enable to distinguish GIST from leiomyomas or schwannomas.

According to Miettinen und Lasota, the postoperative prognosis of patients with gastric GIST can be predicted based on the following clinicopathological parameters: tumor location, tumor size and mitotic rate/5 mm^2 (Table 1). The original population used 50 HPFs to evaluate this area but stated that with newer microscopes bearing larger field diameters an area of 5 mm^2 would be appropriate. Accordingly, the ESMO guidelines from 2012 recommend to evaluate 5 mm^2 instead of 50 HPFs[20-22]. Thus, tumors with a maximum diameter of 2 cm and low proliferative activity have a negligible risk of progression.

EARLY GIST (MICRO-GIST)

Early GIST of the stomach (< 1 cm) differ clinically and pathologically from clinically relevant tumors in that they have a markedly lower proliferation rate. They also occur more often as hypocellular lesions composed of spindle cells and frequently show marked sclerosis. Early gastric GIST (synonym: micro-GIST) exhibit distinctive molecular genetic characteristics: the incidence of *KIT*/*PDGFRA* mutations and particularly *KIT* exon 11 mutations is significantly lower in early than in clinically manifest GIST. There is a high frequency of unique mutations that have thus far not been found in clinically relevant GIST. A large Italian study identified five new mutations,

Table 1 Risk of progression for gastric gastrointestinal stromal tumors according to Miettinen

Tumor parameters		Risk of tumor progression
Mitosis rate	Size	
≤ 5/5 mm^2	≤ 2 cm	0%
≤ 5/5 mm^2	> 2-5 cm	1.90%
≤ 5/5 mm^2	> 5-10 cm	3.60%
≤ 5/5 mm^2	> 10 cm	12%
> 5/5 mm^2	≤ 2 cm	ND
> 5/5 mm^2	> 2-5 cm	16%
> 5/5 mm^2	> 5-10 cm	55%
> 5/5 mm^2	> 10 cm	86%

According to Miettinen *et al*[20-22]. ND: No data.

three in KIT (p.Phe506Leu, p.Ser692Leu, p.Glu695Lys) and two in PDGFRA (p.Ser847X, p.Ser667Pro), as well as four double mutations[5]. These mutations apparently only cause low proliferative activity in GIST. There are also mutations consistent with clinically relevant GIST[23].

Prognosis of patients with early GIST of the stomach

Clinical progression of early gastric GIST (< 1 cm) has not yet been described in the world literature. Thus early gastric GIST generally show benign behavior irrespective of the mitotic rate and exhibit distinctive histopathological and molecular biological characteristics[5]. The GIST-specific prognosis of patients with early gastric GIST is excellent.

CLINICAL MANAGEMENT

Surgical resection of gastric GIST

Surgical R0 resection is the standard treatment for symptomatic gastric GIST and for those larger than 2 cm in diameter. An option in primary inoperable cases is neoadjuvant imatinib therapy with the aim of achieving secondary operability[20,24,25].

Drug therapy of gastric GIST

Drug therapy with a tyrosine kinase inhibitor is indicated in patients with distant metastases[20,25]. Patients with local disease undergo initial R0 resection followed by risk stratification based on tumor location, size, and mitotic activity[22]. A 3-year course of imatinib therapy is the current standard in patients with an intermediate or high risk of tumor relapse and the appropriate mutation analysis[26]. In a controlled phase-3 study, imatinib significantly prolonged survival in GIST with a high risk of progression[26]. Both the ESMO and NCCN guidelines recommend this type of therapy for GIST patients with a significant risk of relapse[20,25]. While evidencebased recommendations are available for the treatment of clinically manifest GIST, there are no uniform guidelines for clinical management of early gastric GIST. Rossi *et al*[5] recently reported that patients with early gastric GIST have an excellent prognosis irrespective of the mitotic rate. Epidemiological data also demonstrate the generally benign behavior of early GIST of the stomach. Rossi et al. coined the term "self-limiting tumorigenesis" to describe the tumor biology of early GIST of the stomach.

Surgical resection of early gastric GIST most likely is overtreatment in older people. The well-documented, generally benign behavior and the high prevalence of early gastric GIST in the elderly argue for a conservative management. Particularly in older patients, it is important to consider not only the hospital morbidity but also the low but not negligible perioperative mortality, which may amount to 1% or higher according to the published literature[27,28]. There are no clinical studies that have demonstrated any advantage (in quality-of-life or in survival) of surgery over endoscopic surveillance in patients with early (< 1 cm) gastric GIST[6].

ENDOSCOPIC SURVEILLANCE

Endoscopic surveillance should be performed in patients with early asymptomatic GIST of the stomach. Repeat endoscopic ultrasound at 12-mo intervals is generally recommended. If the size remains constant, the intervals can probably be extended in the elderly. Interestingly to note, rapid progression of a gastric GIST that had stayed stable at a size of 1.8 cm for 8 years has been reported[29].

If initial cytohistological assessment of early gastric GIST has not been performed or has not been conclusive and if there is strong clinical suspicion of early GIST, endoscopic ultrasound of the stomach should be repeated already after an interval of 2-3 mo. This short interval is not due to the (very low) probability of rapidly progressive GIST[30] but takes into account the (low) risk of a subepithelial lesion different from GIST. The correct evaluation of a subepithelial lesion by endoscopic ultrasound relies on an experienced team of endoscopists. Indeed the differential diagnosis of "subepithelial or submucosal lesions" of the stomach is complex and extensive[10,14]. The differential diagnosis has to include cysts, pseudocysts, varices, ectopic pancreatic tissue, leiomyomas, schwannomas, lipomas, lymphomas, gastric polyps, inflammatory fibroid polyps, submucosal metastases, protruding aneurysms, large lymph nodes, granular cell tumors and gastric carcinoids[31]. Even localized protrusion of the gallbladder, spleen or left liver lobe can appear as a submucosal lesion in conventional gastroscopy.

If the first repeat endoscopic ultrasound (2-3 mo after initial diagnosis) reveals no change in size of a small (< 1 cm) subepithelial or submucosal lesion, the surveillance interval can be extended to 12 mo. However, a lesion that becomes markedly larger after 2-3 mo requires a definitive (histological) diagnosis and therapy (such as surgical resection). In addition, a gastric GIST that increases in size during follow-up has to be considered for surgery[32] and be discussed on the tumor board.

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REVIEW

Endoscopic ultrasonography for surveillance of individuals at high risk for pancreatic cancer

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Abstract

Pancreatic cancer is a highly lethal disease with a genetic susceptibility and familial aggregation found in 3%-16% of patients. Early diagnosis remains the only hope for curative treatment and improvement of prognosis. This can be reached by the implementation of an intensive screening program, actually recommended for individuals at high-risk for pancreatic cancer development. The aim of this strategy is to identify pre-malignant precursors or asymptomatic pancreatic cancer lesions, curable by surgery. Endoscopic ultrasound (EUS) with or without fine needle aspiration (FNA) seems to be the most promising technique for early detection of pancreatic cancer. It has been described as a highly sensitive and accurate tool, especially for small and cystic lesions. Pancreatic intraepithelial neoplasia, a precursor lesion which is highly represented in high-risk individuals, seems to have characteristics chronic pancreatitis-like changes well detected by EUS. Many screening protocols have demonstrated high diagnostic yields for pancreatic pre-malignant lesions, allowing prophylactic pancreatectomies. However, it shows a high interobserver variety even among experienced endosonographers and a low sensitivity in case of chronic pancreatitis. Some new techniques such as contrast-enhanced harmonic EUS, computer-aided diagnostic techniques, confocal laser endomicroscopy miniprobe and the detection of DNA abnormalities or protein markers by FNA, promise improvement of the diagnostic yield of EUS. As the resolution of imaging improves and as our knowledge of precursor lesions grows, we believe that EUS could become the most suitable method to detect curable pancreatic neoplasms in correctly identified asymptomatic at-risk patients.

Key words: Endoscopic ultrasonography; Pancreatic cancer; Surveillance

Core tip: In the era of early diagnosis and screening programs, endoscopic ultrasound (EUS) represents the most promising tool able to identify pancreatic precursor neoplasms in high risk individuals. If compared to other imaging techniques, it is highly accurate to diagnose small pancreatic cancer and pre-malignant lesions, with very low rate of complications and limitations. Here are reported the current role of EUS in various international screening programs and its future possible developments.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related death in the western world[1,2], with a median age at diagnosis of 71 years and 45220 new cases and 38460 deaths in 2013 in the United

States[3]. In contrast to other causes of cancer death (lung, colorectal, breast and prostate), which have declined in the last years, the death rate from PDAC has increased during the same time period[4]. It is a highly aggressive tumor characterized by an incidence rate almost equaling the mortality rate and an overall 5-year survival of approximately 5%-6%[1,2]. This dismal prognosis is mainly due to the fact that the tumor is characterized by a locally advanced or metastic stage at the presentation, low resection rates and poor response to radiotherapy and chemotherapy.

Even though complete resection improves median survival, at the time of diagnosis only 10% to 25% of pancreatic cancer patients will be amenable to potentially curative resection[5]. Also in this case 5-year survival remains low (10% to 24%)[6,7].

However, longer survival has been reported for complete resection of early stage tumors thus identifying patients who have early, small, localized tumors at presentation could improve this poor overall survival rate[8].

Resection of small tumors (< 2 cm or T1) improves 5-years survival (30% to 60%)[9,10]. However it has been alluded that the better prognosis is for tumors < 1 cm (T1a) with 5-years survival up to 78%[6,11,12].

To date, however, it might be difficult to detect such a small pancreas cancer, mainly due the fact that more than 90% of PDAC measuring 1 cm or less in diameter are asymptomatic.

Probably the only way to improve survival lies in identifying early disease or precursor lesions through a screening program of asymptomatic individuals.

As premalignant stages of disease have been identified, and the sensitivity of pancreatic imaging has improved with endoscopic ultrasound (EUS) and high-resolution magnetic resonance imaging (MRI), early detection of small curable pancreatic cancers and premalignant lesions now seems possible[13-16].

Unfortunately, due to the overall low incidence of the disease, accounting for 3% of all new cancer cases in the United States and a life-time risk of 1.3% in the general population, and the lack of simple, safe, accurate, inexpensive, and non-invasive diagnostic tests for early lesions, a widespread screening program does not seem feasible at present.

Multiple risk factors for pancreatic cancer development have been identified like male gender, obesity, African-American or Ashkenazi Jewish descent, nickel exposure, smoking, lack of physical activity, and calorie intake[17-20].

Beside them, also members of a family with a strong history of disease or individuals with inherited pancreatic cancer syndromes, carrying a known genetic mutation, should be considered at high risk of developing pancreatic cancer (high risk individuals, HRIs)[21-25]. Screening of these high-risk groups seems to be of benefit since genetic susceptibility and familial aggregation are responsible of 3%-16% of pancreatic cancers[26-28].

These individuals can be divided into two groups: those who belong to families in which pancreatic cancer affects at least two first-degree relatives without a known genetic mutation (familial pancreatic cancer, FPC) and those with hereditary syndromes or diseases that predispose to the development of pancreatic cancer (Table 1).

FAMILIAL PANCREATIC CANCER

The former represents the largest proportion of hereditary PDAC.

Prospective studies demonstrated an increased risk of pancreatic cancer in healthy first degree relatives (FDRs), related to the number of family members affected. This risk has been estimated to be 2.3 to 4.5-fold greater in individuals with one FDR with pancreatic cancer, 6.4-fold greater in individuals with two FDRs with the disease and 32 to 57-fold greater in individuals with three or more FDRs affected[29-32].

Similarly to other familial tumors, the median age of presentation in patients with FPC is up to 20 years earlier than in patients with sporadic cancer (49 years *vs* 61 years)[33-35] with an "anticipation phenomenon" in the affected kindred and a trend to become more severe and appear at an earlier age as the disorder is passed from one generation to the next[35,36]. Currently, the genetic etiology of most cases of FPC remains undetermined but complex segregation analysis of these patients has led to the discovery of various candidate pancreatic cancer susceptibility genes such as BRCA2 (6%-17% of cases)[37,38], partner and localizer of BRCA2 (PALB2) (1%-4% of cases)[39,40] and palladin, even if mutations of the latter have been identified in normal controls as well[41-43].

Due to the complex nature of pedigrees, a Mendelian risk prediction tool for PDAC, named PancPRO was developed in 2007.

This is a prediction model for FPC that, using full pedigree data and age of family members, estimates the probability that an asymptomatic individual will develop the disease[44].

INHERITED PANCREATIC CANCER SYNDROMES

Individuals with certain tumor syndromes have a marked increase in risk of developing pancreatic ductal adenocarcinoma.

These syndromes are represented by familial atypical mole-multiple melanoma, Peutz-Jeghers syndrome, hereditary pancreatitis, cystic fibrosis, familial breast-ovarian cancer, hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, Li-Fraumeni syndrome.

Familial atypical mole-multiple melanoma

Familial atypical mole-multiple melanoma (FAMMM) is an autosomal dominant disease associated with mutations within CDKN2A gene (p16 Leiden)[45,46]. Its inactivation is associated with PDAC that was found 13 to 38-fold more frequent than expected[46,47], with a cumulative risk

Table 1 Genetic diseases associated with pancreatic cancer risk

Risk condition	Relative risk	Risk by age 70	Gene
Familial pancreatic cancer			*PALLD*
1 first-degree relative	2.3-4.5	2%	*BRCA2*
2 first-degree relatives	6.4-18	3%	*PALB2*
⩾ 3 first-degree relatives	32-57	16%	
Familial atypical multiple mole melanoma	13-38	15%-20%	*CDKN2A/p16*
Peutz-Jeghers Syndrome	132	11%-60%	*STK11/LKB1*
Hereditary pancreatitis	50-87	30%-75%	*PRSS1*
			PRSS2
			SPINK1
			CTRC
Cystic fibrosis	5.3	<5%	*CFTR*
Familial breast ovarian cancer	3.5-10	5%	*BRCA2*
	2.3-3.6	1%	*BRCA1*
Hereditary non-polyposis colon cancer	2.3-8.6	3%-4%	*MLH1*
			MSH2
			MSH6
Familial adenomatous polyposis	4.5-5	2%	*FAP*
			MUTYH
Li Fraumeni sindrome	Unknown	Unknown	*TP53*

by age 75 of 15% to 20%[48,49].

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal dominant genetic disease characterized by an increased risk of various neoplasms, including pancreatic cancer[50,51] and it is often associated with mutations within *STK11* gene, a tumor suppressor gene. Patients with PJS have a 132-fold increased risk[50] and an 11%-36% cumulative risk of developing PDAC with an early age of onset (average: 40.8 years)[50,52]. In this kind of patients, it frequently develops through IPMN[23,53].

Hereditary pancreatitis

Hereditary pancreatitis (HP) is an inherited form of chronic pancreatitis characterized by mutations within *PRSS1*, *PRSS2*, *SPINK1*, *CFTR* and *CTRC* genes[54,55]. PDAC is often a consequence of this condition[56,57] insomuch so resected pancreata from patients with HP frequently demonstrated PanIN-3 lesions (50%)[58]. Patients with hereditary pancreatitis have a 53 to 87-fold increase risk[57,59] with an age of onset at 50 years in smokers[60]. Lifetime risk is 30% to 75% in patients with paternal inheritance[57,59].

Cystic fibrosis

Cystic fibrosis (CF) is a disorder associated with mutations within CFTR gene with an increased risk for PDAC (5.3-fold)[61], in fact the histological aspect of CF associated lesions is very similar to that of "classical" chronic pancreatitis, characterized by atrophy of acinar tissue, fibrosis, and inflammation[62,63].

Familial breast-ovarian cancer

Familial breast-ovarian cancer (FBOC) is an autosomal dominant inherited disease due to mutations within *BRCA1* or *BRCA2* genes.

The risk of PDAC among BRCA1 mutation carriers is low (2.3-3.6 fold than general population)[64,65]. Conversely BRCA2 mutation carriers had a 3.5-10-fold increased risk[66,67] and a 5% lifetime risk of pancreatic cancer[67].

Hereditary non-polyposis colorectal cancer

Hereditary non-polyposis colorectal cancer (HNPCC) is an autosomal dominant genetic condition due to the inherited mutations in DNA-mismatch repair genes, such as *MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM*[68]. The estimated relative risk of pancreatic cancer is 2.3 to 8.6-fold higher with a lifetime risk of pancreatic cancer (3%-4%)[69,70]. Carriers of MLH1 mutations have a higher risk than carriers of MSH2 (5.6 *vs* 2.3)[71].

Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant disease of the colon caused by mutations within the gene *APC*. Among FAP pediatric carriers, pancreatoblastoma may represent an extracolonic manifestation of FAP[72]. The relative risk for pancreatic cancer is 4.5 in patients with the syndrome[73] and the lifetime risk 2%[74].

Li-Fraumeni syndrome

PDAC seems to be a part of the cancer spectrum of the Li-Fraumeni syndrome (LFS), a disease caused by mutations within *TP53* gene[63,75]. It is has been estimated that about 1.3% of these patients show pancreatic cancer[63,76].

PRECURSOR LESIONS

The ideal screening method for HRIs should detect small asymptomatic pancreatic cancers and, mainly, benign non-invasive precursor lesions, to allows for curative surgical resection[77,78]. In fact pancreatic carcinogenesis should be intended as a multistep phenomenon with progressive changes from the normal pancreatic ductal epithelium to infiltrating carcinoma[79].

The other three well known precursor lesions are: pancreatic intraepithelial neoplasms (PanINs), intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs)[78-81].

Pancreatic intraepithelial neoplasia

PanINs are usually asymptomatic and are characterized by microscopic papillary or flat, noninvasive epithelial neoplasms that are usually < 5 mm in diameter and confined to the pancreatic ducts[78,82].

According to the degree of cytological and architectural atypia, PanINs are divided into three grades[83]: PanIN-1: minimal atypia; flat (PanIN-1A) and papillary types (PanIN-1B); PanIN-2: moderate atypia; PanIN-3: severe atypia.

The evidence that this kind of lesions are linked to invasive carcinoma is based on clinical associations and

genetic analysis[81,84-86].

Mucinous cystic neoplasms

Mucinous cystic neoplasms (MCNs) are cystic epithelial neoplasms that occur almost in women, lack of communication with the pancreatic ductal system and have a predilection for the body and tail[80,87].

Malignancy rates of resected MCNs vary from 6% to 36%[80] and usually resembles common ductal adenocarcinoma.

Intraductal papillary mucinous neoplasms

Intraductal papillary mucinous neoplasms (IPMNs) are a more aggressive neoplasm compared to MCNs. They represent a disorder of the pancreatic ductal system, characterized by cystic dilatation. Clinically, three different varieties exist: main duct type characterized by diffuse dilatation of the main pancreatic duct, branch duct type (IPMN-BD) appearing as dilatation of branch ducts, and mixed-type involving both of them.

These lesions are thought to undergo transformation from adenoma to borderline neoplasms, and finally to carcinoma, similarly as seen with PanINs.

Patients with IPMN-MD have a risk of malignancy of approximately 50%-90%[16,86-89], *vs* 6%-46% in patients with IPMN-BD[16,87,89,90]. In these patients, the risk of malignancy increases with presence of symptoms, mural nodules and size over 3 cm[89]. IPMNs are mainly present in familial pancreatic cancer kindred and in PJS and FAP patients where seems to have a more aggressive biological behavior (increased growth rate and degeneration) compared to sporadic IPMNs[22,91]. IPMNs are more prevalent in high risk individuals than in the general population (16%-42% *vs* 0.2%)[92], moreover they are commonest in specimens from FPC than in sporadic PDAC (33% *vs* 6%)[81].

SCREENING

The goal of screening could be the reduction of pancreatic cancer-related mortality. As previously reported, surrogate end point in pancreatic cancer could be the identification and resection of potentially curable lesions (high-grade precursors and early invasive carcinomas). There is no evidence that diagnosing these lesions will improve survival, but there are data suggesting that resection of very early disease is associated with better prognosis[93,94]. However, no consensus opinion could be reached on the best suitable approach for screening until available imaging modalities and biomarkers will become adequate to detect early stage cancer. Actually, serum markers, computed tomography, magnetic resonance (MRI) ± cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography and endoscopic ultrasound haven't all the features of an effective screening tool[95-100]. Describing the screening modalities is beyond the aim of this review. Whatever the approach a surveillance program should be recommended for patients with a risk of PDAC development greater than 10-fold[22,23,77].

This degree of risk includes family members with ⩾ 3 first-degree relatives with pancreatic cancer and patients with hereditary pancreatitis, FAMMM and PJS.

A screening test should also be performed in individuals with syndromes associated with pancreatic cancer and known high-risk factors, such as cystic neoplasia, duct ectasia, diabetes mellitus, smoking history and chronic pancreatitis[101]. To evaluate the risk to develop pancreatic cancer can be used mathematical models, such as the PancPRO model (see above).

No clear consensus was achieved on when to start screening. It seems reasonable to start at 40-50 years of age (30 years for PJS) or 10-15 years earlier than the younger kindred affected by pancreatic cancer[21,22,96,102].

There is no consensus also on the frequency, because evidence on the natural history and rate of progression of pancreatic cancer in high risk patients is still lacking. However, yearly screening seems to be the most suitable approach[21,22,36,103] even if some centers recommend 3 years intervals in case of negative screening exam and absence of other risk factors associated. A more aggressive protocol can be used for patients with abnormal findings at the last screening[52]. In these cases a subsequent screening could be done every 3-6 mo[22,103] or every 3-12 mo[21,36,100].

The majority of studies have generally used the same imaging test for surveillance as for baseline screening, while others suggest an alternating use of MRI/MRCP and EUS[36,98](Figure 1).

ROLE OF ENDOSCOPIC ULTRASONOGRAPHY

Endoscopic ultrasonography (EUS) is known as a powerful imaging tool for studying pancreatic diseases. In particular it has been described as a very accurate imaging technique for early detection of pancreatic cancer providing high-resolution images of the pancreas without the risk of radiation exposure and identifying mural nodules (focal thickening of the wall in branch duct IPMNs), which are associated with increased risk of malignancy[16,82]. With its high resolution, in experienced hands it is able to detect focal lesions as small as 2-5 mm[22,104-106] with the possibility of taking bioptic samples by fine needle aspiration (FNA) for histopathological examination. EUS has been described as a highly sensitive method for pancreatic malignancy[107], but results for accuracy differ. Early studies have shown a better accuracy in detecting PDAC for EUS compared with dual phase helical CT (97% *vs* 73%, respectively)[108]. This results were also confirmed when EUS was compared with multiphase helical CT (98% *vs* 86%, respectively[107,109]. The prospective CAPS3 study is the first blinded study that compared standardized pancreatic protocol CT, secretin-enhanced MRI/MRCP and EUS for one-time screening in HRIs. It showed that EUS and MRI are better than CT for the detection of small, cystic, pancreatic tumors, with a diag-

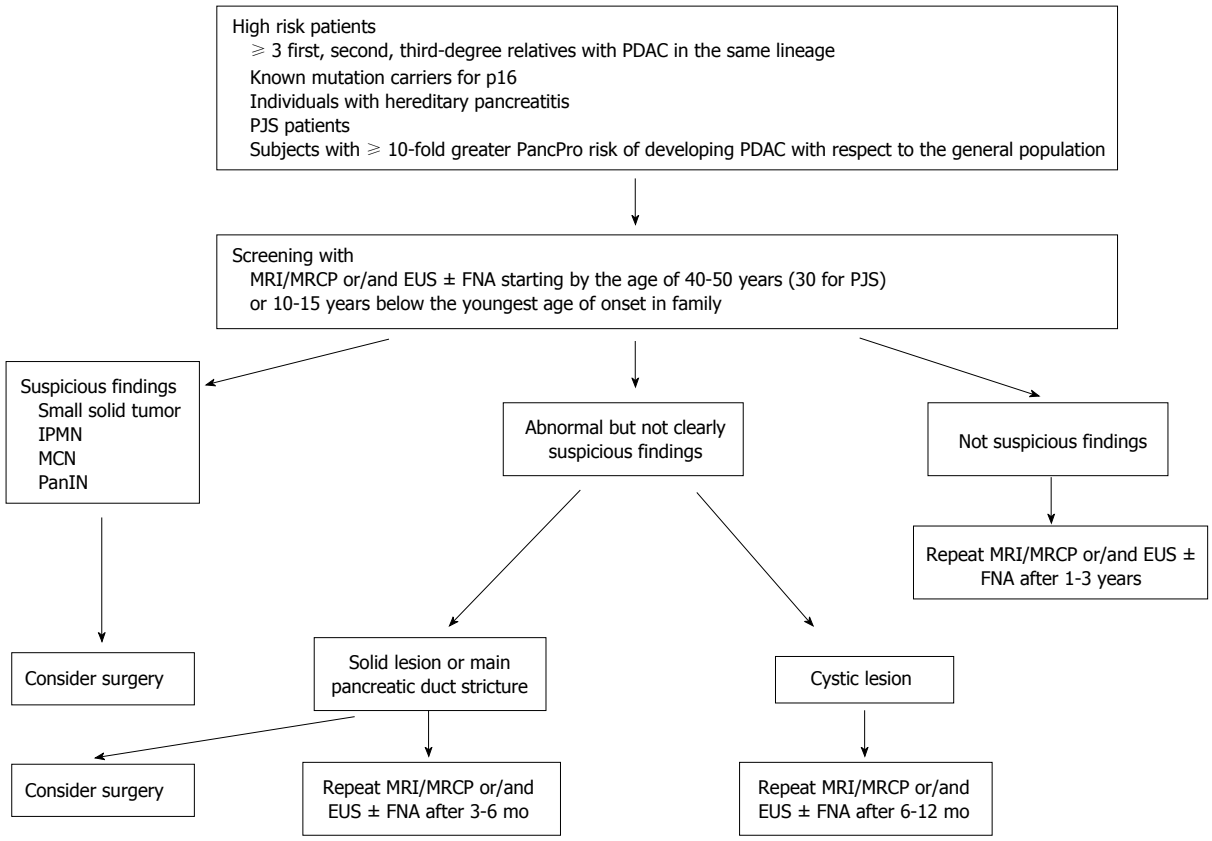

Figure 1 Management algorithm for individuals at risk of pancreatic cancer. EUS: Endoscopic ultrasonography; ERCP: Endoscopic retrograde cholangiopancreatography; CT: Computed tomography; FNA: Fine needle aspiration; PDAC: Pancreatic ductal adenocarcinoma; PJS: Peutz-Jeghers syndrome; MRI: magnetic resonance imaging; MRCP: Magnetic resonance cholangiopancreatography; IPMN: Intraductal pancreatic mucinous neoplasia; MCN: Mucinous cystic neoplasm; PanIN: Pancreatic intraepithelial neoplasia.

nostic yield of 42.6%, 33.3% and 11%, respectively[110]. EUS was also found to be superior to MRI and CT in sensitivity regarding the detection of IPMN-derived and -concomitant PDACs at the first examination (100% *vs* 53% and 53% and 61% *vs* 33% and 39%, respectively) and during a 5 years follow-up period (100% *vs* 50% and 56%, respectively)[111]. In this setting EUS detected PDCAs significantly better than the other modalities and it appears to be more useful than CT and MRI for the early detection of pancreatic cancer (Table 2).

Another recent study[112] has shown an incremental increase in diagnostic yield of EUS-FNA over CT (36%) and MRI (54%) for prediction of a neoplastic cyst and an increase in overall accuracy for diagnosis of neoplastic pancreatic cysts by the addition of EUS±FNA.

A normal EUS examination seems to have a high negative predictive value (NPV)[113]. Two recent studies including patients with suspicion of pancreatic cancer followed for 23.9 and 25 mo, respectively, showed that none of those with a normal EUS evaluation developed pancreatic cancer (NPV = 100%)[114,115].

Furthermore, EUS-guided fine needle aspiration (EUS-FNA) may provide a histological diagnosis of cancer and a means of detecting dysplasia in precancerous lesions[23]. A recent meta-analysis has demonstrated that EUS-FNA is highly sensitive (89%), specific (96%), accurate (97%) and has a very good positive likelihood ratio (16.08) and an acceptable negative likelihood ratio (0.13)[116]. Moreover, another recent study not included in the meta-analysis previously reported[117], confirmed these values and has shown that the diagnostic accuracy of EUS-FNA could be further improved by the addition of pancreatic juice analysis.

EUS complications are rare and the risk of perforation is similar to standard upper endoscopy (< 0.03%). Also EUS-FNA of pancreatic lesions can be considered a safe technique, especially if several technical points are taken into account in each specific situation the endosonographer perform a FNA[118]. The two major complications after a FNA are pancreatitis (0%-2%)[119,120] and bleeding (0% to 1.3%)[121,122], while the risk of infection exists only when mucinous cystic lesions are involved[118]. No deaths were reported[120-123].

Actually, the diagnosis of PanINs by imaging tests is very challenging. The surgical resection of early curable neoplasms detected during screening programs in at-risk individuals has permitted to study the morphology of unadulterated precursor lesions in this kind of patients[21,81]. In particular: (1) PanINs are frequently associated with lobulocentric atrophy and fibrosis; and (2) PanINs are often multifocal.

The combination of these alterations produces grossly appreciable changes in the pancreas with a mosaic of fibrosis, atrophy and uninvolved parenchyma, very similar

Table 2 Endoscopic ultrasound-based studies on screening for individuals at risk for pancreatic cancer

Ref.	No. of patients	High-risk groups	Imaging test	Target lesions	Diagnostic yield	Limits of the study
Brentnall *et al*[21]	14	FPC	EUS + ERCP + CT	PanIN ⩾ 2	50%	
Kimmey *et al*[104]	46	FPC	EUS	PanIN ⩾ 2	26%	
Canto *et al*[22]	38	FPC, PJS	EUS	IPMN, PC	5.30%	Low PPV
Canto *et al*[23]	78	FPC, PJS	EUS	IPMN, PC, PanIN ⩾ 2	10.20%	
Poley *et al*[135]	44	FPC, PJS, FAMMM	EUS	IPMN, PC	22.70%	No pathological confirmation of IPMN
Langer *et al*[103]	76	FPC, FAMMM	EUS + MRCP	IPMN	1.30%	Moderate risk patients
Verna *et al*[162]	51	FPC, FBOC	EUS and/or MRCP	IPMN, PC, PanIN ⩾ 2	12%	
Schneider *et al*[36]	72	FPC, FAMMM	EUS + MRCP	IPMN	12.50%	No pathological confirmation
Canto *et al*[110]	216	FPC, FBOC, PJS	EUS + CT + MRCP	IPMN, PC	39%	Mainly no pathological confirmation

FPC: Familial pancreatic cancer; PJS: Peutz-Jeghers syndrome; FAMMM: Familial atypical multiple mole melanoma; FBOC: Familial breast ovarian cancer; EUS: Endoscopic ultrasonography; ERCP: Endoscopic retrograde cholangiopancreatography; CT: Computed tomography; MRCP: Magnetic resonance chol angiopancreatography; PanIN: Pancreatic intraepithelial neoplasia; IPMN: Intraductal pancreatic mucinous neoplasia; PC: Pancreatic cancer; PPV: Positive predictive value.

to chronic pancreatitis[81,124].

These quite subtle ductal and parenchymal changes are often detectable by EUS using standard criteria for the diagnosis of chronic pancreatitis, such as heterogeneity, multifocal lobularity, echogenic foci, hypoechoic nodules, strands and dilated main and branch pancreatic ducts[22,124,125].

In literature, chronic pancreatitis-like changes are found in variable rates. The John Hopkins group detected these findings in 45% and 61% of the examined HRIs in whom they were significantly more common, compared with control subjects, regardless of age and alcohol exposure[22,23]. This ultrasonographic diagnosis of chronic pancreatitis was surgically confirmed in all but one of the HRIs who underwent surgery. Furthermore, all but 1 of these patients had branch duct-type IPMNs[22]. In the University of Washington study, the authors suggested that the pancreatitis-like changes, which are part of the phenotype of FPC kindreds, are expression of un underlying pancreatic dysplasia rather than chronic pancreatitis[21]. Finally the German group reported a relative low prevalence (22.4%) with all but one normal findings at MRI/MRCP evaluation[103].

These studies suggest that features of chronic pancreatitis should be noted during screening because although the precursor lesions may be too small to visualize by currently available imaging technologies, the effects they produce such as cysts and nodules in a background of intact parenchyma, can be detected by EUS in the hands of an experienced operator.

This was also confirmed in IPMNs. In a recent study conducted on forty patients, who underwent resection for IPMN, PanIN was researched on surgical specimens and the pathological data were compared with endosonography features. EUS changes corresponded to PanIN lesions in 83% of cases and it was able to detect 69% of patients with PanIN lesions (57% of those with panIN-3)[126].

Nevertheless, the presence of a chronic pancreatitis drastically reduces the diagnostic value of EUS, because of the intraductal and parenchymal changes associated with chronic inflammation and fibrosis could not to be differentiated from premalignant pancreatic lesions[127].

In summary the clinical significance of these changes in HRIs remains unclear. They may be indicative of a precursor lesion of PDAC, but these data must be carefully assessed.

Another field of application for EUS in HRIs is in differentiation between focal pancreatitis and pancreatic cancer. Contrast enhanced EUS seems to be a promising technique due to perfusion characteristics of microvessels[128]. Hocke *et al*[129] analyzed the sensitivity and specificity for the diagnosis of pancreatic carcinoma of conventional endoscopic B-mode, power Doppler ultrasound and contrast-enhanced power mode. They reported an increase from 73.2% to 91.1% and from 83.3% to 93.3% respectively, with the use of contrast-enhanced power mode *vs* conventional EUS. The major limits of EUS are: (1) high interobserver variety, even among experienced endosonographers, especially for diagnosis of pancreatitis like changes[130,131]; (2) the need for sedation because of the minimally invasive nature of the procedure; (3) the need of additional clinical and imaging information[112] to improve accuracy as demonstrated by Meining *et al*[132] who reported a worse overall accuracy for a strictly blinded EUS examinations (61.1%) compared to the accuracy of routine and unblinded evaluation with additional imaging information (72.2% and 75.0%, respectively); (4) Low sensitivity in case of chronic pancreatitis, diffusely infiltrating cancer and a recent episode of acute pancreatitis[133,134]; and (5) Low availability outside major centres.

Currently, many international screening protocols are available throughout the world and the majority of them use EUS as the main imaging tool for screening, because of its ability to detect masses < 1 cm[21-23,132,135], with CT or MRI/MRCP scans and ERCP proposed in combination with EUS[136].

The first EUS-based screening program was prospectively conducted by Brentnall *et al*[21] at the Washington University, on a small group of 14 high-risk patients from three unrelated pancreatic cancer kindred that had two

or more affected members in at least two generations. The study evaluates an EUS- and ERCP-based approach with the aim to detect pancreatic cancer precursor lesions (PanINs). The EUS and ERCP suspected signs of PanINs were no specific chronic pancreatitis-like changes. Seven patients (50%) had an abnormal EUS and ERCP histological confirmed as precancerous changes in the pancreas (PanIN-2 and 3) without any invasive cancer.

A follow up study of the same group confirmed a high yield (26%). It was based on a large cohort of 46 patients and was conducted using EUS as the first diagnostic approach, with ERCP for patients with EUS abnormalities. Twelve patients with imaging abnormalities were referred to histological examination and all of them revealed widespread precancerous lesions (PanIN 2 e 3), without evidence of invasive pancreatic cancer[136].

Canto *et al*[23] screened HRIs for early pancreatic neoplasia with an EUS-based and an EUS- and CT-based[22] prospective controlled study at Johns Hopkins University. In the former approach they used EUS to screen 38 asymptomatic individuals from high risk families (≥ 3 affected relatives and PJS). Six pancreatic lesions were detected: four benign masses and two neoplastic (one adenocarcinoma and one IPMN; screening yield of 5.3%). Either the CT or ERCP evaluations did not detect the single PDAC. In the latter one, pancreatic abnormalities were compared in 78 high-risk individuals (72 from FPC kindred and 6 PJS) and 149 control patients. If the EUS was abnormal, EUS-FNA and ERCP were performed. This approach found 8 patients with pancreatic neoplasms (10.2%) confirmed by surgery or FNA (6 patients had benign IPMNs, 1 had an IPMN with invasive ductal adenocarcinoma and 1 patient had PanIN-3) and no pancreatic neoplasia among the control subjects. All of the lesions visualized by CT were also detected by EUS, while CT missed two IPMNs > 1 cm in the second study and one pancreatic cancer in the first one. Moreover, ERCP correctly diagnosed only 2 of the 7 confirmed IPMNs seen by EUS.

In contrast to these findings, Langer *et al*[103] published their results of a prospective screening study conducted by the National German Familial Pancreatic Cancer Registry (FaPaCa) on 76 individuals from 34 FPC and FAMM kindreds. The protocol included CA 19-9 and CEA serum values, EUS, and MRI combined with MRCP at the screening visit. EUS-FNA was performed in the case of indefinite abnormalities and in case of diffuse parenchymal irregularities. Only three serous cystoadenoma, one IPMN, three PanIN 1 and one PanIN 2 were pathologically confirmed. Three of them, the smaller ones, were detected by EUS, but not by MRI. No cancers were identified and only IPMN was considered a significant precancerous lesion for a diagnostic yield of 1.3%.

This lower yield could be explained by the fact that this study included also a large number of patients at a moderate risk (< 10-fold) with a fraction of high-risk patients of 42% *vs* 55% for the second study of the Johns Hopkins University. Moreover, PanIN 1 e 2 and serous cystoadenoma were not considered precancerous lesions. During long term follow-up[36] (24 mo-extended surveillance), this study showed histologically proven precancerous or cancerous lesions in 4 individuals (5.5%) and additional branch duct IPMN in 5 ones, with a diagnostic yield of up to 12.5%, close to the previous rates reported by the Johns Hopkins and the Rotterdam groups.

In comparison, Poley *et al*[135], of the Dutch group, published the results of a prospective study using EUS in 44 asymptomatic high risk family members with FPC, BRCA1, BRCA2, or p16 germline mutation carriers, and patients with PJS. They found asymptomatic PDAC in three patients (6.8%, two with lymph node metastases), and seven IPMNs (16%). Their high yield (22.7%) may be related to the selection of known carriers of mutations at high risk to develop pancreatic cancer with a higher fraction of individuals at elevated risk.

Nevertheless, it has to be pointed out that IPMNs in both German study and in the Dutch study are EUS-diagnosis, not histologically confirmed. The 12.5% and 16% results may as well represent overestimations.

COST EFFECTIVENESS

A screening test can be considered successful if the benefits/costs ratio is favourable. As previously reported, a EUS-based screening allows an early diagnosis of PDAC, while it is not still clear if this approach could be considered cost-effectiveness.

Rulyak *et al*[137] compared one-time EUS-based screening to no screening in a hypothetical cohort of 100 members 50 years old of FPC kindred. The life time medical costs and life expectancy were compared, assuming a 20% prevalence of pancreatic dysplasia and 90% sensitivity of EUS and ERCP. They demonstrated that endoscopic screening of these individuals increases patient life expectancy (38 years, similar to other common preventive medical interventions) in a cost-effective manner ($16885 per life-year saved on the base-case ICER, an indicator which take into account the third-part payer and the societal perspectives). Only patients with a pre-test probability of pancreatic dysplasia of 16% or greater and individuals under 70 years of age seem to have benefits from this approach. Moreover, the sensitivity of EUS and ERCP must be at least 85% in order for screening to be effective. The cost-effectiveness of repeated screening was not determined.

In contrast, Rubenstein *et al*[138] have performed a clinical and economic evaluation of EUS for 45 years-old male first degree relatives with chronic pancreatitis diagnosed by EUS on screening exam. They compared 4 strategies: do nothing, prophylactic total pancreatectomy, EUS and EUS-FNA and assessed mortality, quality of life, complications and costs. They addressed the inferiority of EUS compared to a no-screening approach because of the low sensitivity of EUS in the presence of chronic pancreatitis-like changes. EUS-FNA provided intermediate results. The prophylactic total pancreatectomy could be considered the better approach in terms od life expectancy if the lifetime risk of pancreatic cancer is

46% or greater.

These studies are based on one-time screening and so are not applicable to a individuals who require repeated screening examinations during their life. A review conducted by Latchford *et al*[139] focused on a cost-effectiveness analysis of a screening program in PJS, based on EUS and ERCP for molecular analysis of pancreatic juice. According to this review, patients with suspicious findings would be offered CT, all others should repeat screening 1-3 years later, based on risk stratification detrmined by molecular tests. With this approach over a 35-year period of annual EUS, 3780 screens would be carried out and only those with morphological changes found on EUS are offered CT and ERCP.

This model can give an estimate of costs of about $372708 per life saved. This cost could be further reduced to $297000 per life saved by molecular analysis of pancreatic juice. In this case, in fact, most individuals would only be screened every 3 years thanks to more accurate risk stratification.

FUTURE PERSPECTIVES

In the near future, the development of EUS technology should help us to screen HRIs.

Contrast-enhanced harmonic endoscopic ultrasonography (CH-EUS) visualizes parenchymal perfusion in the pancreas without Doppler-related artifacts[140,141]. It could play a central role associated to EUS-FNA when the latter gives a negative finding in a suspected lesion. Two recent studies[141,142] showed a higher sensitivity of CH-EUS compared to EUS-FNA for the identification of pancreatic carcinoma. Most of false-negative EUS-FNAs resulted to have a hypoenhancement on CH-EUS examination. Moreover, Kitano *et al*[142] found that CH-EUS when combined with EUS-FNA is able to increase the sensitivity from 92.2% to 100% and is superior to MDCT in diagnosing small (< 2 cm) carcinomas, identifying 9 tumours missed by MDCT. Fusaroli *et al*[143] also reported that CH-EUS allowed the detection of small lesions in patients with uncertain EUS findings because of chronic pancreatitis. In addition, CH-EUS allows to focus on the lesion target for EUS-FNA.

Diagnostic accuracy of EUS-FNA will be also enhanced by the detection of DNA abnormalities as k-ras point mutations and microsatellite losses[144,145] or novel protein markers such as mesothelin[146,147] and prostate stem cell antigen[147]. Their detection in EUS-FNA specimens may provide confirmation of the presence or absence of malignancy and should negate the need for further testing.

Characterization of pancreatic cysts has become essential for definitive surgical treatment or ongoing surveillance. However, current diagnostic methods (cross-sectional imaging, EUS, and fluid analysis including cytology, fluid characteristics, chemistry, and tumor markers) do not allow an accurate differentiation between the various types of cysts[148,149]. A novel needle-based confocal laser endomicroscopy (nCLE) miniprobe that can be passed through a 19-G EUS-FNA needle enables real-time imaging with microscopic detail. A pilot study[150] suggests that nCLE can detect mucinous pancreatic neoplasms with excellent specificity and PPV (100% for both of them) but a low sensitivity and NPV (59% and 50%, respectively) with an overall complication rate of 9%.

Finally, computer-aided diagnostic techniques, yet used in some screening programs[151,152], could be added to standard EUS images for the differentiation of pancreatic carcinoma from chronic pancreatitis[151,153]. With digital image processing and computer-aided EUS image differentiation technologies, physicians could use the computer output as a "second opinion" and make the final decisions as reported by the high diagnostic accuracy (98%) of a recent study[154].

CONCLUSION

These data demonstrate that screening with EUS, preferably associated with MRCP, as reported by International Cancer of the Pancreas Screening summit (83.7% agree for EUS and 73.5% agree for MRI/MRCP)[96] is feasible and can detect curable pancreatic neoplasms in correctly identified asymptomatic at-risk patients. In particular, as reported by Ludwig *et al*[155], EUS could be subsequent to an MRCP as initial imaging. This approach should reduce the number of false positives (patients with abnormal MRCPs who on EUS had no appreciable lesion) avoiding unnecessary surgery. The two modalities may complement each other. In fact, MRI/MRCP, in contrast with EUS, is able to image the entire abdomen and pelvis, an useful feature for patients at risk for multi-organ cancer, but has a low sensitivity in detecting PanIN lesions and small (< 1 cm) pancreatic cancer, even if recently there has been the development of 3T MRI scanners able to detects small tumors in asymptomatic patients through indirect signs (black and white sign) and cystic lesions ⩾ 3 mm[99,156]. MRCP is superior to EUS in delineating lesions involving the pancreatic ductal system[97,98] even if a recent study[157] has shown similar results between three dimensional CEUS and MRI in evaluating IPMNs smaller than 1 cm. Nevertheless EUS can image mural nodules associated with increased risk of malignancy.

It is also strongly suggested that surveillance programs should be performed by a center with experience in the specific pathology within the context of peer reviewed protocols to reduce interobserver disagreement[100].

Indeed, EUS is an operator-dependent technique that requires considerable skills and training in EUS is essential to gain experience to reliably examine the pancreas. The intensity and length of training, the requisite curriculum and the minimum number of procedures required to ensure competency are not well-defined[158].

Some experts recommend a minimum of 75 pancreatobiliary procedures and 25 cases of pancreatic FNA[159], others suggest a minimum of 30 supervised EUS-FNA

on pancreatic lesions[160] while someones believe that the majority of trainees will require double the number of proposed procedures to achieve competency in EUS[161,162].

An extensive use of CT or ERCP should be avoided in screening programs that require repeated exams in healthy individuals who have only a statistical risk of cancer.

However, a number of questions remain to be answered. What are the significance and natural history of EUS-detected chronic pancreatitis-like abnormalities? What is the clinical significance of PanIN with moderate dysplasia? Should it always be treated with pancreatectomy? How to manage the IPMN-like cystic lesions frequently found in HRIs? Should be offered surgery or a wait-and-see policy can be adopted?

As the resolution of imaging improves and as our knowledge of precursor lesions grows, we believe that these questions will be answered in the future.

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REVIEW

Advanced endoscopic submucosal dissection with traction

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Abstract

Endoscopic submucosal dissection (ESD) has been established as a standard treatment for early stage gastric cancer (EGC) in Japan and has spread worldwide. ESD has been used not only for EGC but also for early esophageal and colonic cancers. However, ESD is associated with several adverse events, such as bleeding and perforation, which requires more skill. Adequate tissue tension and clear visibility of the tissue to be dissected are important for effective and safe dissection. Many ESD methods using traction have been developed, such as clip-with-line method, percutaneous traction method, sinker-assisted method, magnetic anchor method, external forceps method, internal-traction method, double-channel-scope method, outerroute method, double-scope method, endoscopic-surgical-platform, and robot-assisted method. Each method has both advantages and disadvantages. Robotic endoscopy, enabling ESD with a traction method, will become more common due to advances in technology. In the near future, simple, noninvasive, and effective ESD using traction is expected to be developed and become established as a worldwide standard treatment for superficial gastrointestinal neoplasias.

Key words: Endoscopic submucosal dissection; Traction; Early gastric cancer; Early esophageal cancer; Early colonic cancer

Core tip: Endoscopic submucosal dissection (ESD) is associated with several adverse events, therefore, it requires more skill. Adequate tissue tension and clear visibility of the tissue to be dissected by traction are important for effective and safe ESD like surgery. Many ESD methods with traction have been reported until now. We review these ESD methods not only for early stage gastric cancer but also for early esophageal cancer or colonic cancer. We highlight both advantages and disadvantages of these methods.

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INTRODUCTION

The possibility of expanding the use for endoscopic treatment for early stage gastric cancer (EGC) has been proposed[1]. Endoscopic submucosal dissection (ESD) for EGC has improved the rate of successful *en bloc* resection[2-6] compared to endoscopic mucosal resection (EMR). ESD enables resection *en bloc* for larger lesions, those with ulceration, and those located in difficult sites. Therefore, ESD has been established as a standard treat-

ment for EGC in Japan and has spread worldwide. This method has been used not only for EGC but also for early esophageal and colonic cancers. However, ESD is associated with several complications, such as bleeding and perforation, which requires more skill. Traction is a standard method for maintaining a clear field of vision and to facilitate in the cutting of lesions during surgery. Likewise, adequate tissue tension and clear visibility of the tissue to be dissected by traction are important for effective and safe ESD[7-9].

The simplest method to achieve traction is position change[8,9]. The weight of the lesions and fluid injected to the submucosal layer enables the lesions to be hung from the wall of the gastrointestinal tract due to gravity. Endoscopic submucosal dissection becomes easier because the submucosal layer becomes wider and the field of vision becomes clearer. However, it is sometimes difficult because of limitation of position change and extension of the GI tract due to inner gas.

Recent reports on ESD with traction are described in this article (Table 1).

ESD WITH TRACTION IN UPPER GASTROINTESTINAL TRACT

Foremost, Hirao *et al*[10] reported on an EMR procedure using double endoscopes under general anesthesia, which was similar to surgery about 25 years ago. The lesion was grasped and lifted using grasping forceps through the thin endoscope, and submucosal dissection was done using a needle knife through the main scope (Figure 1). This method was revolutionary at that time; however, it was complicated and invasive. It required two endoscopic systems and more than two endoscopists and two assistants. Furthermore, two endoscopes couldnot be moved easily and independently because of their combined diameter. Thereafter, many kinds of less complicated and invasive methods have been developed.

Clip-with-line method

Lee *et al*[8] and Oyama *et al*[11] reported on the clip-with-line method, which is a simple, easy and useful method for traction not only for gastric ESD (Figure 1) but also for esophageal (Figure 2), colonic, and duodenal ESD. A long silk line is tied to the arm part of the clip, and the submucosal side of the target lesion is grasped. The line is pulled very gently. This method creates a clear field of vision. Jeon *et al*[12] and Ota *et al*[13] reported on similar methods. However, the traction direction by the clip-with-line method is limited. The pulley method is useful for pulling the line to the anal or opposite side (Figure 3). The line is captured by the second clip and fixed at the opposite side of the stomach. The first clip can be pulled to the anal side with the second clip acting like a pulley. Li *et al*[14] reported on similar method.

Percutaneous-traction method

Kondo *et al*[15] reported on percutaneous traction-assisted EMR for gastric neoplasias, which requires a laparoscopic port with a trocar (Figure 4). A small snare is introduced into the gastric lumen through a gastric port to grasp and pull the lesions away from the muscularis propria. Thereafter, von Delius *et al*[16] reported on similar methods using a PEG-minitrocar for the gastric mucosa, and Chen *et al*[17] reported on methods using a looped insertion wire for the esophageal lesions. The loop end of the wire inserted through the PEG route was grasped using biopsy forceps and pulled into the esophagus. The wire was fixed on the proximal edge of the resected mucosa with a clip. The wire was gently pulled out through the PEG route, and the edge of the resected mucosa pulled away from the muscle layer. Nishiwaki *et al*[18] reported on transgastrostomic endoscopy-assisted ESD after percutaneous endoscopic gastrostomy. A small-caliber endoscope was inserted through the mature gastrostomy, and the edge of the resecting specimen was grasped to achieve traction. However, these methods are invasive and cannot be used for lesions on the anterior wall or high fundus of the stomach. They are also sometimes difficult to control the traction direction.

Magnetic anchor method

Kobayashi *et al*[19] and Gotoda *et al*[20] reported on a magnetic anchor system. The magnetic anchor with magnetic weight and microforceps is placed at the mucosal edge. ESD is done with suitable tension by using a high-power electromagnet placed outside the body. However, this system requires large and expensive instruments.

External forceps method

Imaeda *et al*[21,22] reported on ESD using external grasping forceps. An external pair of grasping forceps is used with a second pair (Figure 5A). This method is useful for creating a clear field of vision due to not only pull but also push and gravity, for lesions in the gastric body but also for those in the antrum (Figure 5B); however, for lesions in the cardia and the lesser curvature or posterior wall of the upper gastric body, this method is sometimes difficult. This procedure does not require any assistant to hold the forceps during ESD because the handle is locked. One endoscopist can easily and independently move the endoscope and forceps. Moreover, this procedure can also enable release and regrasping of the lesion with the forceps if the traction is not sufficient. Great care must be taken to avoid damaging the mucosa, especially at the esophagocardial junction, and the overtube is necessary. Although the traction direction is limited, the forceps can always be used to raise the grasped side of the lesion.

Internal traction method

Several internal traction methods have been reported. A

Table 1 Advantages and disadvantages of the traction endoscopic submucosal dissection methods

	Traction			Other advantages	Other disadvantages
	Push	Control of direction	Control of tension		
ESD with traction in upper gastrointestinal tract					
Clip-with-line method[8,11-14]	-	-	+	Simple, easy	
Percutaneous-traction method[15-18]	+	+	+	Regrasping	Invasive
Magnetic anchor method[19,20]	+	+	+		Large and expensive
External forceps method[21,22]	+	-	+	Regrasping, no need of assistant to hold the forceps	Care of mucosal damage
Internal traction method[23-25]	-	-	-	Easy	Roll back of mucosa
Spring-assisted ESD[26]	-	-	-	Easy	
Double-channel-scope method[28]	+	+	+	Regrasping	Synchronous movement of forceps and scope
R-scope[29-31]	+	+	+	Regrasping, swing of knife	Thicker and heavier scope, synchronous movement of forceps and scope
Outerroute method[33-38]	+	+	+	Regrasping	Synchronous movement of forceps and scope, small distance between forceps and knife
Double-scope method[10]	+	+	+	Regrasping	Interference of scopes, two light sources, double manpower
Morita[39]	+	+	+	Regrasping, a little interference of scopes	Thicher overtube, two light sources, double manpower
Higuchi[40]	+	+	+	Regrasping, one light source	Interference of scopes, double manpower
Robot-assisted method[42-44]	+	+	+	Regrasping	More complicated, no response of hemostasis
ESD with traction in colon and rectum					
Sinker-assisted method[45]	-	-	+	Easy	Retreival of scope
External forceps method[46]	+	-	+	Regrasping	Retreival of scope, only rectum
Internal traction method[47-50]	-	-	-	Easy	
Outerroute method[51]	+	+	+	Regrasping	Synchronous movement of forceps and scope
Double-scope method[52,53]	+	+	+	Regrasping	Two light sources and double manpower, interference of t scopes, lesions in only sigmoid colon and rectum
Fusaroli[54]	+	+	+	Regrasping, much cheaper, one light source	interference of scopes, lesions in only sigmoid colon and rectum
Endoscopic surgical platform[55]	+	+	+	Regrasping, freedom offering surgical triangulation	more complicated configuration with fixed instruments, only rectum

ESD: Endoscopic submucosal dissection.

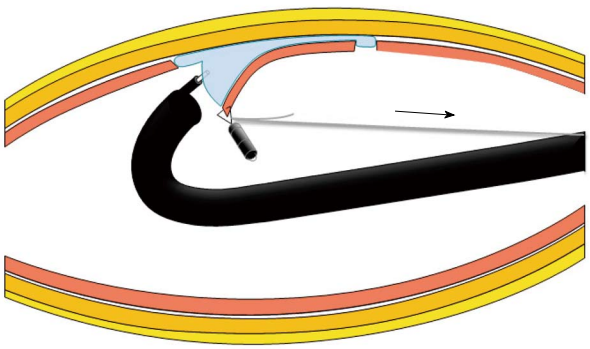

Figure 1 Schema of clip-with-line method.

set of two clips connected by a rubber ring or a nylon line is used. The first clip connected by a rubber ring or nylon line is attached at the target part after circumferential incision. Parra-Blanco *et al*[23] reported the clip-band method. Matsumoto *et al*[24,25] reported on a new traction device called "medical ring". This device is mounted by connecting it to a hemoclip with 3-0 silk. The second clip is attached at the opposite sides of the lesions (Figure 6A). This method pulls up the lesion and opens the resection margin. Since lesions roll back, the traction direction and elevation of the submucosal layer is not sometimes sufficient. Sakurazawa *et al*[26] reported on spring-assisted ESD (Figure 6B). One end of the stainless-steel spring device (length 20 mm) is fitted with a polyurethane loop and the other end is fitted with a clip, which was attached to the opposite side. The spring lengthens by more than 10 fold in this range. However, the spring device is made of stainless steel, and its safety within the intestinal tract has not been established. Chen *et al*[27] reported on the nylon line method using 2 hemoclips. However, this method might not be applicable for neoplasms in the py-

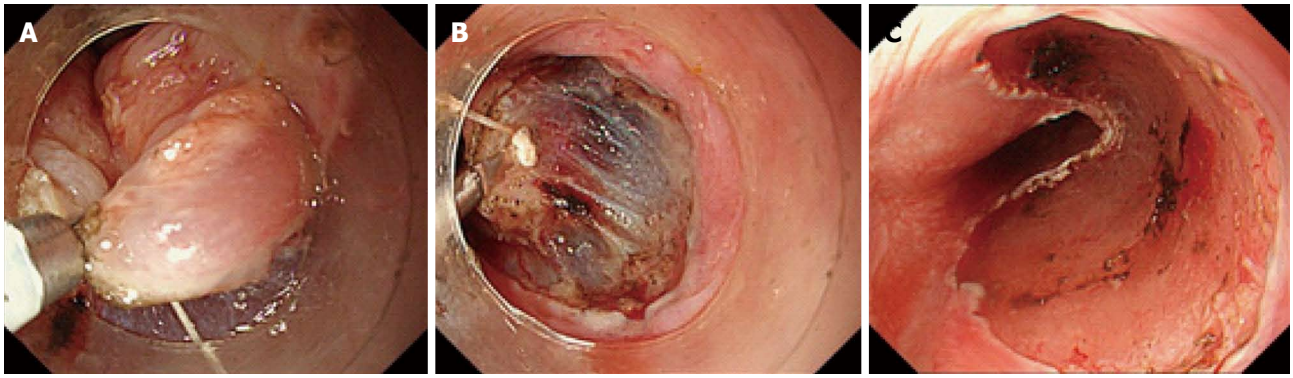

Figure 2 Clip-with-line method. A: Submucosal side of the target lesion in the esophagus was grasped using clip tied to long silk line; B: When the line was pulled very gently, submucosal layer was elevated; C: Lesion was dissected *en bloc*.

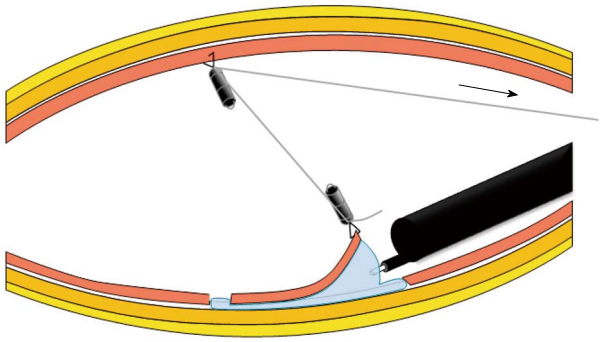

Figure 3 Schema of pulley method. The first clip with the line can be pulled to the anal side with the second clip, which is fixed at the opposite side.

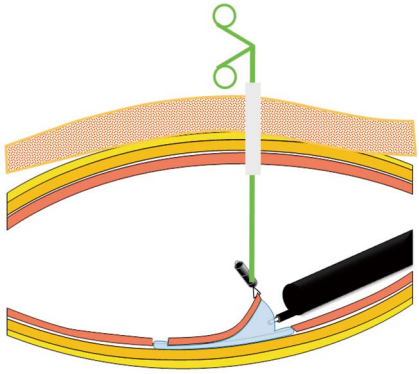

Figure 4 Schema of Percutaneous-traction method. A small snare is introduced into the gastric lumen through a gastric port to grasp and pull the lesions.

lorus or cardia, where space is limited, and control of the traction power is sometimes difficult.

Double-channel-scope method

A pair of grasping forceps inserted into a channel of a double-channel scope can create traction during ESD. Ishigooka *et al*[28] reported on endoscopic resection with injection of hypertonic saline epinephrine using a double-channel scope (S-ERHSE). Yonezawa *et al*[29] reported on ESD using an R-scope, which has two movable instrument channels: one moves a pair of grasping forceps vertically for lesions with traction and the other swings a cutting knife horizontally for dissection (Figure 7). Neuhaus *et al*[30] and Lee *et al*[31] also reported on this method using the R-scope, which facilitated ESD of large gastric areas. Even though the concept was good, the endoscope required a significant learning period to enable proficiency in its use. The forceps moves synchronously with the scope, therefore, it is sometimes difficult to control the traction direction. Hijikata *et al*[32] reported on ESD using the outer sheath of an injection needle. The bottom of the dissected mucosal layer is pushed and lifted up using the injection sheath through one channel to reveal the submucosal layer and ensure adequate traction, and submucosal dissection was conducted by an IT-knife through the other channel. However, a double-channel scope is thicker, heavier, and more difficult to manipulate than a single-channel endoscope. Moreover, since the grasping forceps or the outer sheath is inserted through the endoscope, it moves synchronously with the endoscope, which sometimes makes it difficult to control the traction direction and to cut the submucosal layer of larger lesions.

Outerroute method

Motohashi *et al*[33,34] reported on ESD using the Impact Shooter®, which is mounted on the scope (Figure 8). The mucosa was hold with the forceps through the channel which was connected to the Impact Shooter®, and the submucosal tissue was dissected with the hook knife. However, the forceps moves synchronously with the endoscope and the distance between forceps and knife is not sufficient; therefore it is sometimes difficult to control the traction direction. Okamoto *et al*[35] and Tsao *et al*[36] reported on ESD using a clip with a nylon suture through a thin tube. The plastic sheath allows the endoscope to be easily maneuvered without interrupting the traction. Ohata *et al*[37] reported ESD using a biopsy forceps, which is straight when closed and curved when opened. It was inserted a long straw tube which was mounted on an overtube, and the edge of the targeted lesion was grasped and lift up. Teoh *et al*[38] reported on

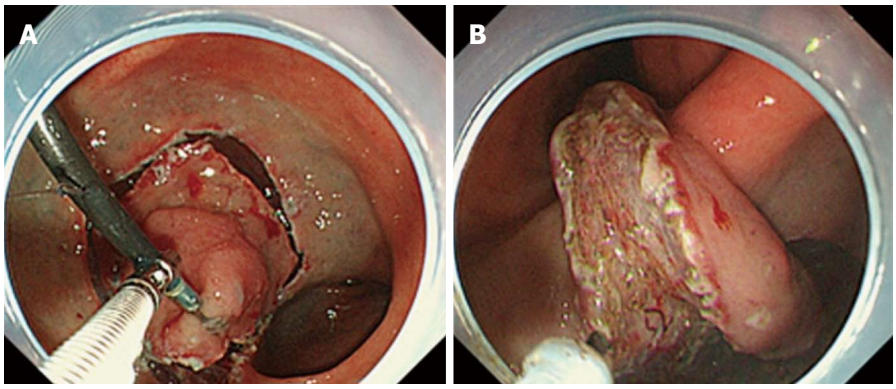

Figure 5 Endoscopic submucosal dissection using external forceps. A: External grasping was anchored at distal margin of lesion in the lesser curvature of the antrum under control of endoscope and second grasping forceps; B: With gentle oral traction applied with external grasping forceps, submucosal layer was dissected in retroversion from aboral side.

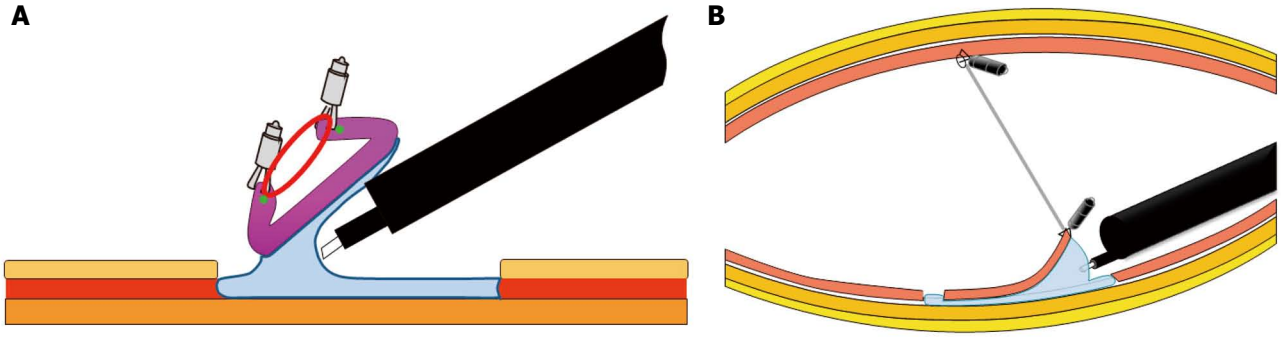

Figure 6 Schema of Internal traction method. A: The second clip is attached at the opposite sides of the lesions; B: The second clip is attached at the opposite sides of the stomach.

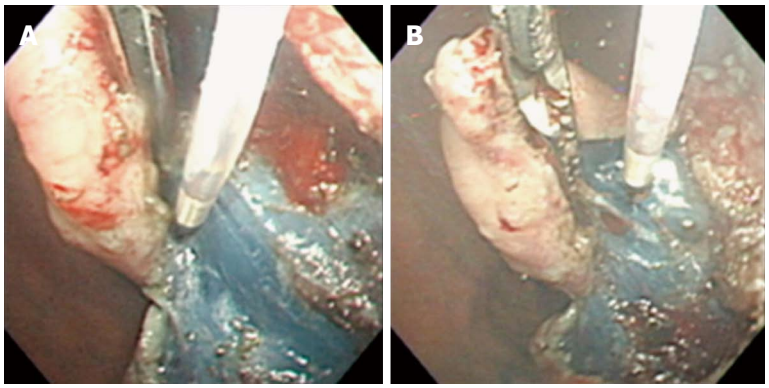

Figure 7 Endoscopic submucosal dissection using double-channel R-scope. A: R-scope has two movable instrument channels: one moves grasping forceps vertically for lesion with traction and other swings cutting knife horizontally for dissection; B Cutting knife was horizontally swung.

ESD using the Endolifter®, which consists of a retractable grasping forceps attached to a transparent cap by a hinge that allows simultaneous grasping, retracting, and lifting of the mucosa. However, these methods reduce the sideway movements of the endoscope due to retraction at a fixed point by the forceps, this in turn limits the maneuverability of the endoscope. The visual field is limited due to masking of the dissected part of the mucosa for large lesions.

Double-scope method

Since Hirao *et al*[10] reported on an EMR procedure using double endoscopes; several methods using a second thin endoscope have also been reported. The traction direction can be controlled easily with the double-scope method (Figure 9). However, the second scope sometimes limits the maneuverability of the main scope because of their combined diameter. Moreover, this method requires two light sources and more than

Figure 8 Schema of outerroute method.

two endoscopists and two assistants. Morita *et al*[39] described a double-endoscope method, which requires two light sources and a specially designed overtube with two channels to prevent interaction between two endoscopes. However, the overtube is thicker than the usual one. Higuchi *et al*[40] reported on another method without an overtube, which requires only one light source that can be transferred between two endoscopes, eliminating the problem of optical interference. After circumferential incision, the main scope is left in the stomach, and the light source is removed and attached to the thin endoscope. The thin endoscope is inserted along the main endoscope, and the lesion is grasped along its margin using grasping forceps. Thereafter, the light source is removed from the thin endoscope and reattached to the main endoscope, and submucosal dissection is done. However, the disadvantage is the same as the double scope method except for only requiring one light source. A thin trans-nasal endoscope-assisted ESD has been reported by Ahn *et al*[41]. This method has disadvantages, including nasal bleeding due to trans-nasal access, invasion due to double endoscopes, need for two endoscopists, and temporary hindrance of movement between endoscopes.

Robot-assisted method

Ho *et al*[42], Wang *et al*[43], and Phee *et al*[44] reported on ESD using a Master and slave trans-luminal endoscopic robot (MASTER). The MASTER consists of three major components: a master robotic controller, a telesurgical workstation, and a slave manipulator. The system is designed to work with a therapeutic endoscope with two operating channels. The master controller is the human-machine interface that controls the slave manipulator, a unilateral electromechanical device that responds to the operator's input and drives the end-effectors, grasper, and monopolar electrocautery hook. This method is similar to laparoscopic surgery. However, the disadvantage of the MASTER is its more complicated configuration with fixed instruments. If massive bleeding from a resected site occurs, it is necessary to change the therapeutic endoscope to a conventional endoscope to conduct hemostasis using hemoclips or hemostatic forceps.

ESD WITH TRACTION IN COLON AND RECTUM

ESD using traction for lesions on the colon and rectum is similar to that for lesions on the UGI tract. However, the lumen in the colon and rectum is narrow and bending. Moreover, for lesions in the proximal colon, reinsertion after retrieval of the endoscope is more time-consuming in some methods compared to that for lesions in the UGI tract. Therefore, lesions in only the rectum or sigmoid colon are indicated in some methods.

Sinker-assisted method

Saito *et al*[45] reported on sinker-assisted ESD for colorectal cancer. The sinker system is composed of a metallic clip attached to a 1-g sinker by a short nylon line. The metallic clip is attached to a target site at the edge of the exfoliated mucosa. The traction direction is controlled using gravity by changing the position of the body. A limitation of this method is the necessity of retrieving the scope to set up the sinker system.

External forceps method

Imaeda *et al*[46] reported on ESD using external biopsy forceps that are bendable (Figure 10). This procedure is similar to ESD using external grasping forceps for EGC[21,22]. The external bendable forceps was introduced with the help of the grasping forceps. After the external forceps was anchored at the anal margin of the lesion, with bending and gentle anal traction applied with the forceps, the lesion was elevated. However, it is used only for rectal cancers because of the difficulty in inserting and controlling the forceps in the colon.

Internal traction method

Sakamoto *et al*[47,48] reported on ESD using a S-O clip (Sakamoto and Osada clip). The S-O clip consists of a metal clip attached to the end of a spring or a rubber strip, its other end of which a double nylon loop is connected to. A spring S-O clip is attached to the edge of the exfoliated mucosa and a regular clip is used to grasp the distal nylon loop and applied to the colon wall opposite the lesion. Osada *et al*[49] also reported on ESD using a loop-attached rubber band, which consists of a circular rubber band connected to many nylon loops. Tomiki *et al*[50] reported on ESD using latex band traction. These methods are easy, safe, and noninvasive, and the instrument can be used at any location.

Outerroute method

Okamoto *et al*[51] reported on ESD using a clip with a nylon suture through a thin tube. This procedure is similar to ESD using a clip with a nylon suture through a thin tube for EGC[35]. However, this method needs a single balloon overtube, which enables the endoscope to be retrieved and inserted to set up the devices. The forceps moves synchronously with the endoscope and the distance between forceps and knife is not sufficient, therefore, this method limits the maneuverability of the endoscope. The visual field is limited due to masking of the dissected part of the mucosa for large lesions.

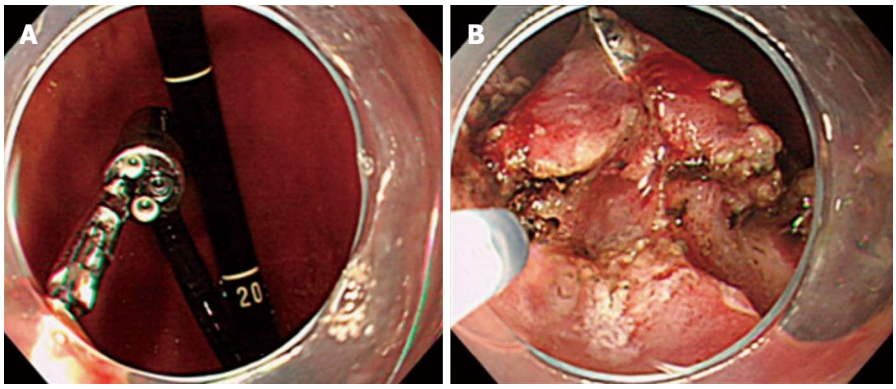

Figure 9 Endoscopic submucosal dissection using double-endoscopes. A: Lesion was grasped and lifted using grasping forceps through thin endoscope; B Submucosal dissection was done using needle knife through main scope.

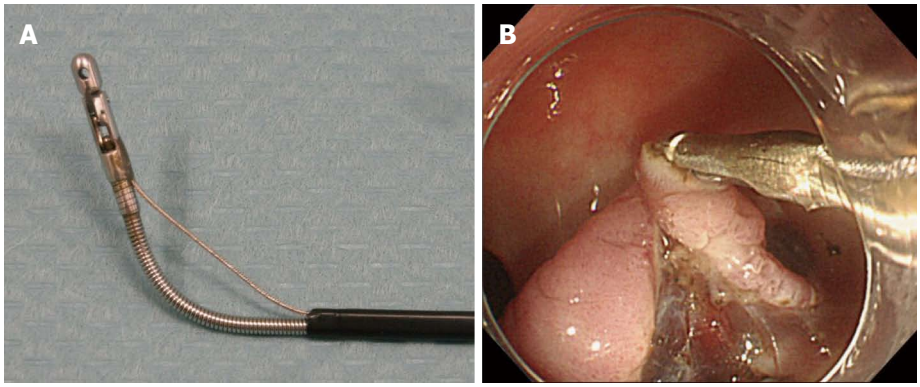

Figure 10 Endoscopic submucosal dissection using external forceps. A: Bendable biopsy forceps; B: Bending forceps and traction applied using forceps elevated lesion and widened submucosal layer.

Double-scope method

Uraoka *et al*[52,53] reported on a double-scope method for large colorectal tumors. An endoclip is attached to the edge at the exfoliated mucosa, a second thin endoscope is then inserted into the lumen followed by removal of the primary endoscope. A snare is used to grasp the positioned endoclip and pull the lesion away from the muscle layer. Once again, the primary endoscope is inserted to the location of the lesion. However, this method is limited to the rectum and rectosigmoid colon because of the difficulty in intubating the second endoscope to the oral side of the distal sigmoid colon. It requires a second endoscopist to operate the traction system. It also may be difficult for treating larger lesions, like the circumferential ones because of insufficient space to maintain the necessary cutting line view provided by the traction system. Fusaroli *et al*[54] reported on a double-scope method using a prototype blind multi-bending thin probe with a working channel of 2.8 mm. It is much cheaper (when on the market) and more resistant to shear stress than a pediatric scope. However, it is limited to treating lesion on the rectum or sigmoid colon. Two endoscopists and three nurses (one for care of the patient, one for handling accessories for main endoscope and one for handling accessories for the second endoscope) are required.

Endoscopic surgical platform

Diana *et al*[55] reported on ESD using an endoscopic surgical platform, the Anubiscope®, equipped with two working channels for surgical instruments with four degrees of freedom offering surgical triangulation and ESD using a robotic version of the Anubiscope®. However, it is limited to treating lesion on the rectum, and is a more complicated configuration with fixed instruments.

PERSPECTIVES FOR FUTURE

Although many kinds of ESD methods with traction have been reported, each method has not only some advantages but also the other disadvantages. Some methods require retrieving the scope to set up devices, others are limited to lesions in certain areas, directions and tension of traction, and still others are somewhat complicated and invasive. If each knife or a grasping forceps be moved independently, as in surgery, and the direction and tension of traction can be controlled at will, ESD with traction might become easier and more flexible. A grasping forceps with flexible bending function, which is thinner than an ultrathin endoscope, may make ESD with traction easier.

If robotic endoscopy, which enables ESD with traction, advances in technology in the near future, it may make ESD easier, may approach to the lesions in any area regardless of gastric movement due to respiration, and may also enable endoscopic hemostasis.

CONCLUSION

Simple and flexible methods with traction can make ESD easier and safer. In the near future, simple, noninvasive, and effective ESD with traction is expected to be developed and become established as a standard treatment for superficial gastrointestinal neoplasias worldwide.

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Laparoscopic management of gastric gastrointestinal stromal tumors

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most frequent gastrointestinal tumors of mesodermal origin. Gastric GISTs represent approximately 70% of all gastrointestinal GISTs. The only curative option is surgical resection. Many surgical groups have shown good results with the laparoscopic approach. There have not been any randomized controlled trials comparing the open *vs* laparoscopic approach, and all recommendations have been based on observational studies. The experience obtained from gastric laparoscopic surgery during recent decades and the development of specific devices have allowed the treatment of most gastric GISTs through the laparoscopic approach.

Key words: Gastrointestinal stromal tumors; Laparoscopy; Surgery; Stomach; Gastrectomy

Core tip: Gastrointestinal stromal tumors (GISTs) are the most frequent gastrointestinal tumors of mesodermal origin. Gastric GISTs represent approximately 70% of all gastrointestinal GISTs. The only curative option is surgical resection. Many surgical groups have shown good results with the laparoscopic approach. There have not been any randomized controlled trials comparing the open *vs* laparoscopic approach, and all recommendations have been based on observational studies. The experience obtained from gastric laparoscopic surgery during recent decades and the development of specific devices have allowed the treatment of most gastric GISTs through the laparoscopic approach.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most frequent gastrointestinal tumors of mesodermal origin[1], and gastric GISTs represent approximately 70% of all gastrointestinal GISTs[2]. These tumors are derived from the interstitial cells of Cajal[3], and have been shown to harbor gain of function mutations in the cell-surface KIT receptor in approximately 90% or in the platelet-derived growth factor receptor α (PDGFRA) in 8%[4].

Most tumors are limited to the primary organ, and less than 2% of tumors present lymph node metastasis. GISTs can also metastasize to the peritoneum and infrequently present hematogenous metastasis to other intra-abdominal viscera, lung, pleura, bone and brain[5].

Most patients are asymptomatic; the tumors are usually found as an incidental finding in 4%-39% of cases[6-11]. In most surgical series, the most frequent symptoms are gastrointestinal bleeding (14%-68%), abdominal pain (16.1%-45%), abdominal mass (3.3%-21%), early

satiety (36%), anemia (19.4%-77%), weight loss (11%), bowel obstruction (3.6%), liver metastasis (3.6%), dyspeptic symptoms (9.7%) and dysphagia (9%)[6-10]. There is a clear relationship between tumor size and symptoms, smaller tumores are generally asymptomatic[4].

The diagnosis is usually made by endoscopy or abdominal imaging. During endoscopy, it is possible to see gastric lumen narrowing associated with normal protruded mucosa, although in larger tumors, the mucosa can show ulcers due to local ischemia[12,13]. The ideal method for diagnosis is endoscopic ultrasonography (EUS), which can define the size, vascular pattern and form of the tumor and differentiate between an extraluminal compression and a submucous growth. GISTs are hypoechoic tumors located at the fourth layer, although some reports have shown tumors located at the third layer. However, the imaging of these tumors is not sensitive (43%), which necessitates histologic evaluation. EUS also helps guide fine needle aspiration biopsies, showing better performance than biopsies under normal endoscopy[12]. The sensitivity of FNAB guided by EUS increases by 10% if a pathologist makes an immediate examination of the adequacy of the sample[13]. In some series, preoperative diagnosis was only possible 52.3%[7].

Computed tomography (CT) is necessary for preoperative stratification. CT can usually show intra- or extraluminal tumors with different morphologic patterns according to size. Larger tumors can show irregular margins and heterogeneous internal density, and if the diameter is larger than 6 cm, the tumors are usually accompanied by central necrosis. Magnetic resonance imaging (MRI) is recommended in cases of simultaneous liver metastasis because of the possibility of conducting a combined resection. PET-CT can be useful in patients with undetermined findings on CT or MRI[14]. However, there is not a good correlation between imaging findings and malignancy[15].

A differential diagnosis with other submucous tumors such as leiomyoma, leiomyosarcoma, schwannoma, granular cell tumors, heterotopic pancreatic tissue, lipoma, neurofibroma, Kaposi tumors and non-functional adrenal tumors should be performed[16,17]. Immunohistochemistry for GIST detection is very useful and shows positivity for CD117 (95% of GISTs)[16]. Only 2% are usually related to PDGFRA mutations[16,18]. Other helpful tests are CD34 that is positive in 70% of the cases and vimentin[16].

SURGICAL TREATMENT

The only curative option is surgical resection, which can be offered to patients with good functional status and non-metastatic resectable tumors, although in some cases, a metastasis resection surgery can be performed in association with resection of the primary tumor[19]. Surgical principles for resection include total extracapsular resection, avoiding tumor fracture or bleeding, which are associated with recurrence and peritoneal sarcomatosis[20]. There are no recommended margins, because microscopic margins status doesn´t correlate with survival as does the mitotic count and tumor size. Wedge resection is a good option for tumors located in the anterior wall or greater curve. For tumors located at the antrum wedge resection can produce a stenosis, so formal gastric resections are favored. Wider margins have not shown any oncologic advantage[21], and lymph node dissection has not been indicated[22]. The National Comprehensive Cancer Network (NCCN) guidelines suggest that tumors smaller than 1 cm that do not fulfill high risk endosonographic criteria (irregular borders, cystic spaces, ulcer of echogenic heterogeneous focus) can be observed during endoscopic follow-up at each 6-12-mo interval[23]. Most larger tumors need adjuvant treatment with imatinib mesylate to avoid recurrence[2].

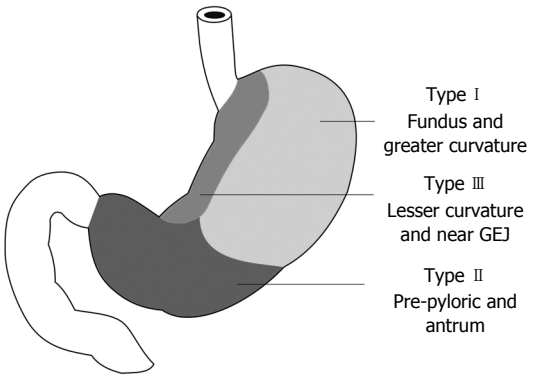

Figure 1 Surgical approach according to gastrointestinal stromal tumor localization.

LAPAROSCOPIC TREATMENT

Open surgical resection was the standard of treatment until two decades ago. Many surgical groups have shown good results with the laparoscopic approach. Although NCCN guidelines suggest that laparoscopic resection is indicated in tumors less than 2 cm, many surgeons have reported a safe excision of tumors > 5 cm and other up to 10 cm[24-26]. Lukaszczry and Pretez in 1992 were the first to report a successful laparoscopic resection of a gastric GIST[27].

The laparoscopic techniques can be divided into different subtypes: transgastric resections, endoscopy-assisted laparoscopic resections, wedge resections, partial gastrectomy and hand-assisted laparoscopic resections[24]. The surgical approach depends on tumor size and location (Figure 1). Privette *et al*[25] proposed a classification system based on tumor location as a guideline to choose the best surgical approach. Trocars and operating tables are organized in a similar manner to any other hiatus procedures, with the surgeon located between the legs. A 12-15 mmHg pneumoperitoneum is established, and a 30° camera and a liver retractor are useful. Before resection, it is mandatory to review the abdominal cavity to rule out peritoneum or liver metastasis. If the surgeons

Table 1 Non-comparative series of laparoscopic resection of gastric gastrointestinal stromal tumor

Ref.	*n*	Age (yr)	Tumor size	Tumor localization	Type of surgery	OR time (min)	Notes	Complications/ conversions	Follow-up (mo)
Privette *et al*[25]	12	60.5	5.2 cm PG 4.6 cm TransG 5.5 cm DG	5 Fundus or greater curvature 3 Prepyloric or antral 5 Lesser curvature	5 PG × Lap 3 DG × Lap 5 TransG × Lap	PG 180 (122-262) DG: 322 (256-340) TransG: 236 (202-265)	9/12 GIST 1 Schwannoma 2 Leiomiomas LOS: GP: 3.4 GD: 8.3 GT: 3.3	16.6% complication 1 Enterotomy 1 GI Bleeding No conversions	Only specified for 5 pts
Sexton *et al*[32]	61	59.1 ± 19	3.8 ± 1.8 AR: 229.7 NAR 140.9	Fundus 19 Antrum 18 Body 17 GE junction 7 Pylorus 2	PG 52 DG 4 TotGas 3 TransG 3	151.9 ± 67.3	LOS: 3.9 ±2 LOS AR: 3.9, NAR: 4.1	16.4% complication No conversions 1 POP death	15 (0-103) 3 recurrences
Berindoague *et al*[9]	22	66.7	5.6 (2.5-12.5)	Upper third 6 Middle third 7 Lower third 10	GP 13 1 LAP-HA TotGas 1 LAP TotGast 1 LAP-HA GD 1 TransG	NR	18/22 GIST 1 Adenomyoma 1 Hamartoma 1 Plasmocytoma 1 Parasitic Tumor (anisakis) LOS 6 (4-32)	18.2% complication 3 Delayed gastric emptying 1 Intestinal Obstruction 2 Conversions (9.1%)	32 m (1-72) 1 recurrence
De Vogelaere *et al*[24]	31	63.8	4.4 (0.4-11)	Anterior gastric wall 23 Others not specified	31 PG	99	LOS 8.5	3.2% Complication 1 POP Bleeding	56.3 No recurrences
Hwang *et al*[10]	63	52.8	3.5 GE Junction 3.4 Prepyloric Size of other tumor not specified	7 GE junction Upper third 22 Middle third 11 Lower third 19 4 Prepyloric	3 DG 37 PG 23 TransG (5 Enucleations)	86.1 ± 43.7	LOS 5.3 ± 1 1.8 41 GIST 8 Leiomyoma 4 Carcinoids 1 Liposarcoma 6 Heterotopic Pancreas 2 Hyperplastic Polyps 1 Parasitic Infection	4.7% Complication 1 Staple line bleeding 1 SSI 1 Staple line dehiscence	14.9 (2-42) No recurrences
Novitsky *et al*[26]	50	60 ± 13	4.4 ± 2.0 cm	GE Junction 8 Cardias 9 Anterior Wall 10 Posterior Wall 4 Greater Curvature 6 Lesser Curvature 3 Antrum 4 Prepyloric 6	TotGas 1 DG 2 PG 40 LAP/END 4 LAP-HA 3	135 ± 56	LOS 3.8 ± 1.6	8% 4 Minor complications	36 (4-84) 4 recurrences
Lai *et al*[2]	28	56.9 ± 12.4	3.4 ± 1.6	Upper third 13 Middle third 8 Lower third 7	28 PG	189.6 ± 79.5 Stapled 194.3 ± 50.5 Hand-Sewn	LOS 6.7 ± 1.8	3.5% conversion	43.3 ± 23.5 No recurrences
Choi *et al*[36]	23	59.7 ± 8.3	4.2 ±2.1	Upper third 13 Middle third 5 Lower third 5	23 PG	104.3	LOS 5.2 ± 2.3	4.3% complication 1 Delayed gastric emptying No conversions	61 (7-98)
Nguyen *et al*[22]	28	65	4.6 (0.4-11.5)	LAP PG 22 Subtotal Gastrectomy 3 OS (Converted) : TotGas 1 Intraluminal excision 1 1 Not specified	23 GP × LAP 3 GD × LAP 1 GT × LAP 1 TotGas × CA (converted)	143 (46-336) This includes Small Bowel GIST resections. No data only on gastric resections	LOS 4 (1-50 d)	9% complications 11% 3 conversions Mortality 1 POP death This includes Small Bowel GIST resections. No data only on gastric resections	NS
Huguet *et al*[37]	33	68	3.9 (0.5-10.5),	GE Junction 5 Body 24 Antrum 4	PG 29 LAP-HA PG 4	124 (30-253)	LOS 3 (1-40)	9% complications 2 POP Bleeding 1 SSI 6% conversions	13 (3-64) No recurrences

Ronellenfitsch *et al*[38]	17	56 (43-79)	2.9 (0.8-6)	11 Not specified 6 Antrum	17 PG	130 (80-201)	LOS 7 (5-95)	11.8% Complications: Staple leaks 5% conversion (peritoneal adhesions)	18 (1-53) No recurrences
Tagaya *et al*[39]	15	65.3 (52-75 years)	TransG 2.9 (1.7-6.5) GP 3.9 (1.2-8)	TransG: Upper third 4 Middle third 1 Lower third 1 PG: Greater curvature 2 Lesser curvature 1 Anterior wall 2 Middle third Ant wall 1 Middle Third Post wall 1	TransG 8 PG 7	TransG:168 (132-211) PG: 121 (60-190)	LOS TransG: 8.8 (7-12) LOS PG: 9.6 (7-14)	No complications	After final Pathology only 9 tumors were GIST TransG 18-73 PG: 6-122 No recurrences

GLA: Gasless laparoscopy-assisted; PG: Wedge Resection or Partial Gastrectomy; DG: Distal Gastrectomy; TransG: Transgastric Gastrectomies; TotGas: Total Gastrectomy; OS: Open surgery; AR: Anatomic resections; NAR: Non-anatomic resections; LOS: Length of stay; NS: Not specified; LAP/END: Laparoendoscopic resection; LAP-HA: Laparoscopic hand-assisted; RG: Remnant Gastrectomy; Prox Gas: Proximal Gastrectomy; SSI: Surgical site infection.

suspect solid organ metastasis, the use of intraoperative ultrasound with biopsy can help in the operative decision. Assistance by endoscopy during the surgical procedure is useful for locating the tumor and guiding resection, and staining with ink could help delineate the resection margins.

Tumors located at the fundus and at the anterior and posterior walls can be resected by partial gastrectomy or wedge resection. In cases of small tumors, the greater curve is mobilized, ligating the gastroepiploic vessels with an ultrasonic scalpel or a thermal device. The gastric wall is elevated with sutures placed in the seromuscular layer around the tumor to obtain a complete resection with a linear mechanical stapler, guaranteeing macroscopic margins. In cases of larger tumors, the gastric wall is directly opened and the tumor is resected, maintaining a free margin with a late direct closure using a continuous suture. In cases where tumors are located in the posterior wall, an anterior gastrotomy is made exactly above the tumor, usually assisted by endoscopy. The tumor is resected by the techniques described, with a late closure of the anterior wall with a continuous suture[11,26].

For tumors located at the antrum or at the prepyloric area, partial gastrectomy is recommended due to the high risk of stenosis and delayed stomach emptying when wedge resections are used. In these cases, the greater and lesser curves are dissected to obtain retrogastric access. The duodenum is sectioned just distal to the pylorus with a linear mechanical stapler, and the proximal section is also made with a mechanical stapler; this is usually assisted by endoscopy. Finally, a Roux-en-Y anastomosis is made[25].

Tumors located at the esophagogastric junction are infrequent and represent less than 5% of all tumors. Some authors have recommended enucleation of these tumors based on the high morbidity (6%-24%) and mortality (0%-1.5%) with classical resections and due to the lack of advantage in prognosis and survival[28]. However, the best surgical approach is still debated[29]. The enucleation is made through an anterior gastrotomy, and in these cases, a submucous infiltration with epinephrine is recommended to avoid bleeding and perforation. The use of devices such as an ultrasonic scalpel or an electrocautery has been recommended[10,28].

Some authors have varied the surgical technique using transgastric trocars and endoscopy-assisted insufflation. In these cases, smaller tumors can even be extracted by the mouth using endoscopy[25]. For larger tumors, other authors have suggested a hand-assisted technique because it allows for better exploration and easier handling and dissection of the tumor[12,13]. Others have also shown good results with the single-port approach or dissections without insufflation[8]. In all cases, the use of a bag is recommended for the extraction of the tumor to avoid recurrence and metastasis at the port insertion sites[30,31].

Until now, there have not been any randomized controlled trials comparing the open *vs* laparoscopic approach, and all recommendations have been based on observational studies. Actual recommendations are based on outcomes related to surgical technique (intact specimen, free margins) and prognosis (operative complications, recurrence, cancer free survival)[32] reported from these observational studies. Tables 1 and 2 show the results of comparative and non-comparative published series.

Recently, Koh *et al*[33] published a systematic review of eleven observational studies comparing laparoscopic *vs* open resection with evaluation of short and long term

Table 2 Comparative series of laparoscopic resection of gastric gastrointestinal stromal tumor

Ref.	*n*	Age	Tumor size	Tumor localization	Type of surgery	OR time (min)	Notes	Complications/ conversions	Follow-up (mo)
Wu *et al*[8]	28	61.6 GLA 60.7 CA	2.6 ± 1 1.8 GLA 2.5 ± 1.0 CA	Anterior fundus: 5 GLA 5 CA Posterior fundus: 6 GLA 2 CA Anterior body: 3 GLA 3 CA Posterior Body: 1 GLA 3 CA	15 GLA 13 OS All were Wedge Resections	GLA 129 ± 36.1 CA 110.8 ± 38.1	GLA Less POP Pain during the first 3 d Earlier oral intake Less LOS 5.8 *vs* 7.2 días	7.1% complication 1 OS Ileus 1 Enterotomy during GLA corrected during LAP	NR
Catena *et al*[7]	21	50.1	4.5 ± 2.0	Body 16 Antrum 4 Fundus 1	21 PG	151 ± 56	LOS 4.8 ± 1.6	No intraoperative complications	35 (5-58)
	25	54.6	6.2 ± 1.9	Body 17 Antrum 6 Fundus 2	25 OS (PG)	134 ± 33	LOS 7.1 ± 1.2	No differences in complications	91 (80-136) 1 recurrence
Melstrom *et al*[31]	46 17 LAP 29 OS	62 Lap 60 OS	OS 6.39 82.1-10) LAP 4.27 (1.5-9.1)	Lap: Upper third 6 Middle third 10 NS 1 OS: Upper third 6 Lower third 22 NS 1	17 PG 24 PG × OS 4 DG × OS 1 TotGas × OS	Lap 135 OS 157	LOS: OS 6.25 LAP 2.68 I	Complications OS: 13.8% LAP: 11.8% 6% conversion	OS 59 4 recurrences LAP 32 No Recurrences
De Vogelaere *et al*[11]	53		Total 5.9					LAP : 2.7% 1 Pulmonary Embolism	Lap 83
	37 LAP	LAP 63.7 ± 15.4	LAP 5.6	Not specified	Not specified	LAP 48.5 ± 16	LOS Lap 7		No Recurrences LAP
	16 OS	OS 63.7 ± 10.7	OS 7.5	Not specified	Not specified	OS 155 ± 48.1	LOS OS 14	OS 18.7% complications: Pneumonia 1 Anastomotic Ulcer 1 Fistula 1	OS 71 6 recurrences CA
Karakousis *et al*[40]	80	68	OS 4.3 (2-9)	OS : Fundus 7	OS 39 PG 1 DG	OS 89	LOS: LAP 4 OS 7	Complications OS 25% LAP 14%	LAP 28 (0.3-70 m) Recurrences 1 LAP
	OS 40		LAP 3.6 (0-7-7.8)	Body/antrum 32 Pylorus 1 Lesser curvature 12	LAP 40 PG	LAP 96		32.5% Conversions	OS 43 (0.1-139) Recurrences 1 OS
	LAP 40			LAP: Fundus 3 Body/antrum 37 Pylorus 0 Lesser curvature 10					
Kim *et al*[41]	104	59.8 ± 10.5	5.1 ± 3.3	Upper third 61	Technique according to procedures was NS	LAP 91.1 ± 57 CA 165.8 ± 75.6	LOS LAP 4.6 ± 2.3 CA 9.8 ± 4.1	1% Complications 1 Delayed Gastric Emptying	49.3 (8.4-164.4) Recurrences 5 No Difference in recurrences between OS and LAP
	LAP 80			Middle third 24					
	OS 24			Lower third 19	99 PG 5 TotGas				
Silberhummer *et al*[21]	63 OS 41 LAP 22	62.3 ± 14.4	CA 5.8 ± 4.0 LAP 3.5 ± 1.4	Body 29 Antrum 18 Fundus 10 GE Junction 6	OS: PG 32 DG 5 RG 4 LAP 19 Tumorectomy 3 PG	135 ± 56	LOS LAP 7.8 (± 3.1) LOS CA 12.8 ± 5.0	4.7% complications: 1 Gastrocutaneous Fistula 1 Catheter Sepsis 1 POP Ileus LAP: 18.2% conversions	37 ± 27.9 Recurrences in 4 (7%)
Nishimura *et al*[42]	LAP 39	62	LAP 3.8 (0.8-7.3)	LAP: Upper third 19 Middle third 16 Lower third 4	LAP GP: 12 LAP-HA 17 TransG 10	LAP: 136 min OS: 115 min	NR	No Complications Conversion Rate 2.6%	LAP: 18.9 (2.6-96.4) Recurrences 4 LAP

	OS 28		OS: 4.2 (2.0-7.0)	OS Upper third 11 Middle third 11 Lower third 6	OS PG: 19 Prox Gas: 5 TotGas: 3 DG:1				OS: 31.2 (4.4-121.9) 1 Recurrence OS
Otani *et al*[43]	60 OS 22 LAP 38	59 (32-86)	4,25 (1.8-15.0)	Upper third 36 Middle third 20 Lower third 4	LAP: PG: 35 LAP-HA: LAP-HA PG 2 LAP-HA DG 1 OS: PG 11 ProxGas 9 DG 2	LAP 141 LAP-HA 188 CA 197	LOS LAP 7.2 *vs* 13.7 CA	3.3% complications: 1 Gastric Stenosis 1 Anastomotic Leak	53 mo 2 Recurrences

GLA: Gasless laparoscopy-assisted; PG: Wedge resection or partial gastrectomy; DG: Distal gastrectomy; TransG: Transgastric gastrectomies; TotGas: Total gastrectomy; OS: Open surgery; AR: Anatomic resections; NAR: Non-anatomic resections; LOS: Length of stay; NS: Not specified; LAP/END: Laparoendoscopic resection; LAP-HA: Laparoscopic hand-assisted; RG: Remnant gastrectomy; Prox Gas: Proximal gastrectomy; SSI: Surgical site infection.

outcomes. In their study, which included 381 patients in the laparoscopic group and 384 patients in the open group, the laparoscopic approach showed a lower frequency of minor complications (OR = 0.517; 95%CI: 0.277-0.965), lower length of stay [mean difference -3.421 d (-4.737 to -2.104)], shorter time to the initiation of oral diet [mean difference -1.887 d (-2.785 to -0.989)] and lower intraoperative bleeding [mean difference -86.508 mL (-141.184 to -31.831 mL)]. They could not find any statistically significant differences in reoperation rate, operative time, positive margins, local recurrence, cancer free survival and overall survival. However, comparisons showed that most high risk tumors were treated with open gastrectomy, introducing a selection bias.

The rate of conversion to open surgery is 0%-31%[11], and this cannot be considered a complication but rather an intraoperative decision to obtain better tumor control when the surgeon is faced with adverse intraoperative conditions.

Follow up

Follow-up is mandatory in all patients, even in the absence of malignancy. Patients should be reviewed every 3-6 mo during the first 5 years. An annual endoscopy and CT are recommended to rule out local recurrence[20]. The survival rate of patients with early tumors is greater than 90%[34]. A size larger than 10 cm, a high mitotic rate and intraoperative rupture are risk factors for recurrence[35].

CONCLUSION

The experience obtained from gastric laparoscopic surgery during recent decades and the development of specific devices have allowed the treatment of most gastric GISTs through the laparoscopic approach. As with all surgical techniques, the laparoscopic approach must be applied in select patients with particular characteristics based on functional status, tumor size, location and surgeons' experience. The case series presented in this review support laparoscopic resection as a safe and effective alternative, with similar rates of complications, but with lower pain and an early recovery. It is important to realize that tumor size by itself is not an adequate factor to contraindicate the laparoscopic approach and that other factors should be considered in the decision.

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ORIGINAL ARTICLE

Histology assessment of bipolar coagulation and argon plasma coagulation on digestive tract

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Abstract

AIM: To analyze the effect of bipolar electrocoagulation and argon plasma coagulation on fresh specimens of gastrointestinal tract.

METHODS: An experimental evaluation was performed at Hospital das Clinicas of the University of São Paulo, on 31 fresh surgical specimens using argon plasma coagulation and bipolar electrocoagulation at different time intervals. The depth of tissue damage was histopathologically analyzed by single senior pathologist unaware of the coagulation method and power setting applied. To analyze the results, the mucosa was divided in superficial mucosa (epithelial layer of the esophagus and superficial portion of the glandular layer of the stomach and colon) intermediate mucosa (until the lamina propria of the esophagus and until the bottom of the glandular layer of the stomach and colon) and muscularis mucosa. Necrosis involvement of the layers was compared in several combinations of power and time interval.

RESULTS: Involvement of the intermediate mucosa of the stomach and of the muscularis mucosa of the three organs was more frequent when higher amounts of energy were used with argon plasma. In the esophagus and in the colon, injury of the intermediate mucosa was frequent, even when small amounts of energy were used. The use of bipolar electrocoagulation resulted in more frequent involvement of the intermediate mucosa and of the muscularis mucosa of the esophagus and of the colon when higher amounts of energy were used. In the stomach, these involvements were rare. The risk of injury of the muscularis propria was significant only in the colon when argon plasma coagulation was employed.

CONCLUSION: Tissue damage after argon plasma coagulation is deeper than bipolar electrocoagulation. Both of them depend on the amount of energy used.

Key words: Argon plasma coagulation; Electrocoagulation; Gastrointestinal endoscopy; Surgical procedures; Endoscopic gastrointestinal; Mucous membrane/injuries

Core tip: The best way of applying heat to hollow digestive organs during thermal endoscopic therapy has not been clearly established so far. This study analyzes the histophathological effect of bipolar electrocoagulation and argon plasma coagulation on fresh surgical specimens of the digestive tract. Tissue damage after argon plasma coagulation is deeper than bipolar electrocoagulation. Both of them depends on the amount of energy used.

Garrido T, Baba ER, Wodak S, Sakai P, Cecconello I, Maluf-Filho F. Histology assessment of bipolar coagulation and argon plasma coagulation on digestive tract. *World J Gastrointest Endosc* 2014; 6(7): 304-311 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i7/304.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i7.304

INTRODUCTION

The association of diathermy to endoscopy has provided significant advances in endotherapy, which became a valuable alternative to traditional surgery and therapeutic procedure of choice in several conditions (*e.g.*, sphyncterotomy, polypectomy)[1-3]. Such a safe and cost-effective approach has justified the widespread of gastrointestinal endotherapy. However, reports of severe complications associated to endoscopic coagulation are common[4,5]. Pleural effusion, esophageal and colonic perforation and fistulae have followed argon plasma coagulation[6-8]. A case of colonic perforation has been associated to bipolar coagulation[9]. On the other hand, power setting and time interval of endoscopic coagulation can be very variable among authors[7,10-13]. The best way of applying heat to tissue has not been clearly established for hollow organs so far.

The aim of this study was to analyze the depth of coagulation necrosis caused by bipolar electrocoagulation and argon plasma coagulation on fresh gastrointestinal specimens, using different power settings and time intervals.

MATERIALS AND METHODS

Nine fresh surgical specimens of esophagus, 11 of stomach and 11 of colon were submitted to bipolar electrocoagulation and argon plasma coagulation. Surgical specimens of esophagus, stomach and colon, resected for neoplasic diseases were given to the author in the surgical room, right after the end of surgery. The specimens were kept in saline solution from the time of its removal until its preparation for thermal appliance (median of 3 h). Bipolar electrocoagulation was applied with power settings of 20 W and 50 W, during 1, 3, 5 and 10 s. A 454A Kairos - DNI Nevada Inc.® equipment and 7Fr QuickSilver-COOK® probes were used for bipolar electrocoagulation (Figure 1A). The specimens were also coagulated by argon plasma, with power settings of 50, 70 and 90 W, during 1, 3 and 5 s. An ICC 300 - ERBE® equipment and 7Fr GIT - ERBE® probes were used for argon plasma coagulation. The argon gas flow was set to 2l/min. The probe was kept up to 2 cm from the tissue surface, in an angle of 90°. In the esophagus, the combination of 20 W × 1s for bipolar electrocoagulation and 70 W power setting for argon plasma coagulation were not applied due to less available tissue (Figure 1B).

The depth of tissue damage was histopathologically analyzed by a single senior pathologist unaware of the coagulation method and power setting applied, with the help of an optic microscope (40 ×, 250 × and 400 ×). Citoplasmatic acidofilia, cellular picnosis and the presence of "ghost cells" were the histopathological parameters used to define cellular necrosis (Figure 2).

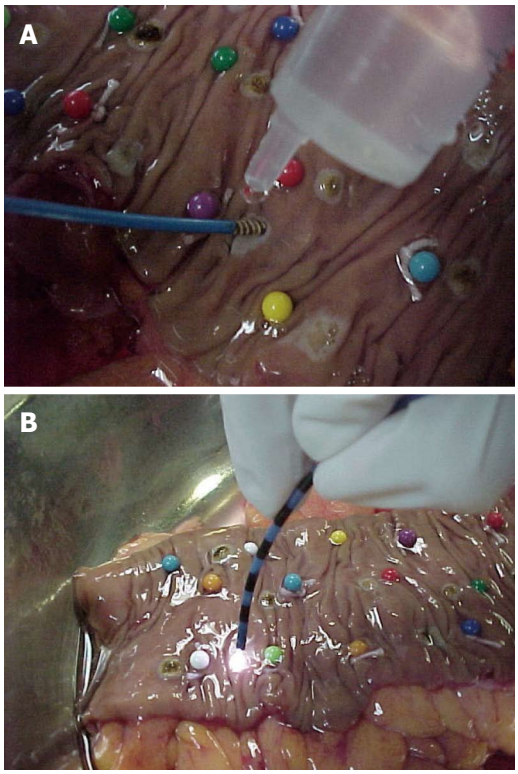

Figure 1 Colon specimen. A: Bipolar electrocoagulation of a colon specimen; B: Argon plasma coagulation of a colon specimen.

Necrosis involvement of the intermediate mucosa, the muscularis mucosa and the muscularis propria of the specimens was observed for the relevance of this stratification in clinical practice.

The intermediate mucosa was considered involved when necrosis was noted until the lamina propria of the esophagus or deep portion of the glandular layer of the stomach and colon. The muscularis mucosa was considered involved when necrosis was present through its whole extension. Muscularis propria was considered involved when any extension of necrosis was present. For both methods, necrosis involvement of the layers was compared in several combinations of power and time interval. Q-square and Fisher´s test were used for the statistical analysis and a level of significance < 5% was adopted.

RESULTS

Macroscopically, coagulated spots from both methods resulted in depressed whitish lesions to brownish ulcerations associated to blisters (Figure 3).

The frequency of involvement of the layers in different combinations of power setting and time interval, in both methods, is shown in Tables 1-6. Involvement of

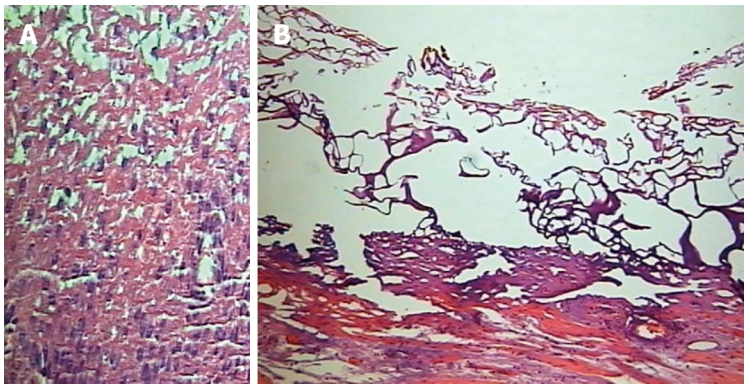

Figure 2 Cellular necrosis. A: "Ghost cells" [hematoxylin and eosin (HE), 250 ×]; B: Citoplasmatic acidofilia and cellular picnosis (HE, 400 ×).

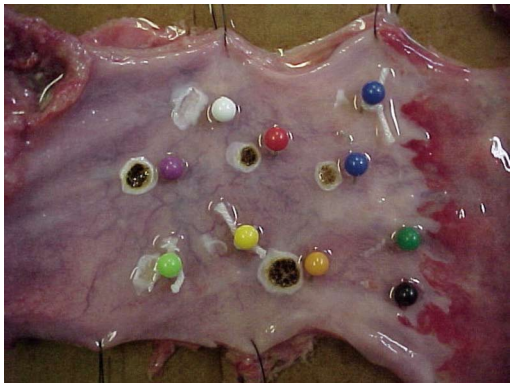

Figure 3 Macroscopic aspects of coagulated spots (both methods).

the intermediate mucosa of the stomach and of the muscularis mucosa of the three organs was more frequent when higher amounts of energy were used with argon plasma. In the esophagus and in the colon, injury of the intermediate mucosa was frequent, even when small amounts of energy were used. The use of bipolar electrocoagulation resulted in more frequent involvement of the intermediate mucosa and of the muscularis mucosa of the esophagus and of the colon when higher amounts of energy were used. In the stomach, these involvements were rare. The risk of injury of the muscularis propria was significant only in the colon when argon plasma coagulation was employed.

Figure 4 show the microscopic aspect of coagulated spots with different depths of coagulation necrosis.

DISCUSSION

The ideal way of applying thermal endoscopic methods to gastrointestinal wall should be deep enough to obtain the therapeutic purpose, as well as avoiding involvement of deeper layers which carries a risk of stenosis, due to healing of muscular layers or even perforation, when muscularis propria is involved.

In the esophageal specimens submitted to argon plasma coagulation, we observed a low incidence of involvement of the muscularis mucosa when the method was applied for short time, being 56% and 67% the frequencies of this involvement for appliances lasting 1 s and 78% to 89% for appliances lasting 3 and 5 s. No significant difference in depth was observed between 50 and 90 W coagulations. Watson *et al*[14] also have not noticed difference in depth related to power setting (from 40 to 99 W), applying the same method in three specimens of esophagus. The involvement of the entire mucosa (including the muscularis mucosa) was also less frequent when argon plasma was applied for shorter time, 52% and 76% for 1 and 3 s, respectively.

Damage to the intermediate mucosa (including the lamina propria) was frequently observed (78% to 89%), independently of the amount of energy used (from 50 to 450 J). As the destruction of the entire mucosa layer is, in theory, the purpose of the endoscopic ablation of Barrett´s metaplasic epithelium, it seems that application of smaller amounts of energy decreases the risk of involvement of the muscularis mucosa, maintaining a good therapeutic result. This is particularly relevant when Barrett involves the whole circumference of the organ, increasing the risk of stenosis. Using argon plasma with 60 W potency for 1 s to destroy Barrett´s Esophagus, Grade *et al*[15] observed intestinal metaplasia below repaired squamous epithelium in 20% of the cases. With this amount of energy they had no complications. Pereira-Lima *et al*[7], Pedrazzani *et al*[6], Schulz *et al*[16] and Ragunath *et al*[17] applied higher amounts of energy of argon plasma, treating patients with Barrett's esophagus (65 to 70 W for 10 s *vs* 90 W for a short interval). Pereira-Lima *et al*[7], Pedrazzani *et al*[6] and Schulz *et al*[16] obtained complete eradication of the metaplastic epithelium, while Ragunath *et al*[17] obtained 65% eradication of the metaplastic epithelium. However, complications as stenosis, pleural infusion, one case of pneumoperitoneum and one case of hemorrhage for ulcer were observed in their series. Injury of the muscularis propria occurred in two coagulation points in our study, when 90 W × 1 s and 50 W × 5 s were used, representing 3.7% of all coagulation points. In Watson´s *et al* study[14], this damage occurred only in 5% of the cases when the time interval was 3 s and Heindorff *et al*[18] described just 1% of perforation when argon plasma was use to permeate esophageal cancer. This shows that despite uncommon, the risk of esophagus perforation with this method exists, even when small amounts of energy are used.

On the stomach wall, argon plasma coagulation resulted in involvement of the intermediate mucosa frequently

Table 1 Involvement of digestive wall layers by argon plasma coagulation in the esophagus

Time	1 s			3 s			5 s		
Power setting	50 W	70 W	90 W	50 W	70 W	90 W	50 W	70 W	90 W
Energy amount	50 J	70 J	90 J	150 J	210 J	270 J	250 J	350 J	450 J
M int	89%	-	78%	89%	-	89%	78%	-	89%
M M	67%	-	56%	89%	-	89%	78%	-	89%
M P	0%	-	11%	0%	-	0%	11%	-	0%

M int: Intermediate mucosa; MM: Muscularis mucosa; MP: Muscularis própria; J: Joule.

Table 2 Involvement of the digestive wall layers by argon plasma coagulation in the stomach

Time	1 s			3 s			5 s		
Power setting	50 W	70 W	90 W	50 W	70 W	90 W	50 W	70 W	90 W
Energy amount	50 J	70 J	90 J	150 J	210 J	270 J	250 J	350 J	450 J
M int	50%[a]	55%[a]	91%	82%	91%	82%	91%	91%	100%
M M	30%[a]	27%[a]	64%	73%	82%	73%	82%	82%	100%
M P	0%	0%	0%	0%	0%	0%	0%	0%	9%

[a]$P < 0.05$ *vs* argon plasma coagulation. M int: Intermediate mucosa; MM: Muscularis mucosa; MP: Muscularis própria; J: Joule.

Table 3 Involvement of digestive wall layers by argon plasma coagulation in the colon

Time	1 s			3 s			5 s		
Power setting	50 W	70 W	90 W	50 W	70 W	90 W	50 W	70 W	90 W
Energy amount	50 J	70 J	90 J	150 J	210 J	270 J	250 J	350 J	450 J
M int	82%	82%	100%	91%	100%	100%	100%	100%	100%
M M	45%[a]	27%[a]	90%	64%[a]	82%	91%	91%	91%	82%
M P	9%	0%	30%	9%	18%	27%	18%	36%	45%

[a]$P < 0.05$ *vs* argon plasma coagulation. M int: Intermediate mucosa; MM: Muscularis mucosa; MP: Muscularis própria; J: Joule.

Table 4 Involvement of the digestive wall layers by bipolar electrocoagulation in the esophagus

Time	1 s		3 s		5 s		10 s	
Power setting	20 W	50 W	20 W	50 W	20 W	50 W	20 W	50 W
Energy amount	20 J	50 J	60 J	150 J	100 J	250 J	200 J	500 J
M int	-	44%	56%	78%	67%	78%	67%	100%
M M	-	22%	33%	44%	22%	67%	44%	78%
M P	-	0%	0%	0%	0%	0%	0%	0%

M int: Intermediate mucosa; MM: Muscularis mucosa; MP: Muscularis própria; J: Joule.

(82% to 100%), when 90 J or more was applied (until 450 J). This energy interval also caused muscularis mucosa injury more often (64% to 100% of cases). In the other hand, the involvement of this layer until 70 J was 27% to 30%. Watson *et al*[14] also noted deeper involvement of the wall when higher power settings for longer intervals were used in three fresh surgical specimens of stomach. However, different stratification of the wall layers did not allow comparisons with our study. Eventual healing retractions of the stomach wall rarely result in clinical manifestation due to the amplitude of its lumen. Indeed, papers describing APC to treat Watermelon Stomach, using 60[19] to 100 W[12] were successful with no complications.

In a similar study, Johanns *et al*[20] described involvement of the muscularis mucosa when 75 W or more, for 5 or 10 s, were applied to the gastric wall. The difference found in our study may be consequent to the small number of specimens of the mentioned study (four). In both papers the involvement of the muscularis propria was rare, being observed only when 90 W × 5 s was applied in ours and 155 W × 10 s was applied in Johann's. These results support the safety of the use of argon plasma coagulation for the treatment of gastric lesions. However as the intermediate mucosa is damaged with the same frequency with 90 J or more, application of higher amounts of energy seems to be unnecessary to treat lesions above the muscularis mucosa. Sebastian´s *et al*[21] results corroborate this theory.

Damage caused by APC to the muscularis mucosa

Table 5 Involvement of the digestive wall layers by bipolar electrocoagulation in the stomach

Time	1 s		3 s		5 s		10 s	
Power setting	20 W	50 W	20 W	50 W	20 W	50 W	20 W	50 W
Energy amount	20 J	50 J	60 J	150 J	100 J	250 J	200 J	500 J
M int	36%	45%	64%	27%	18%	18%	45%	45%
M M	18%	0%	27%	9%	9%	0%	18%	18%
M P	0%	0%	9%	0%	0%	0%	0%	0%

M int: Intermediate mucosa; MM: Muscularis mucosa; MP: Muscularis própria; J: Joule.

Table 6 Involvement of digestive wall layers by bipolar electrocoagulation in the colon

Time	1 s		3 s		5 s		10 s	
Power setting	20 W	50 W	20 W	50 W	20 W	50 W	20 W	50 W
Energy amount	20 J	50 J	60 J	150 J	100 J	250 J	200 J	500 J
M int	64%[a]	60%[a]	55%[a]	100%	91%	100%	82%	90%
M M	9%[a]	30%[a]	27%[a]	55%	55%	82%	64%	60%
M P	0%	0%	0%	0%	0%	0%	9%	10%

[a]$P < 0.05$ *vs* argon plasma coagulation. M int: Intermediate mucosa; MM: Muscularis mucosa; MP: Muscularis própria; J: Joule.

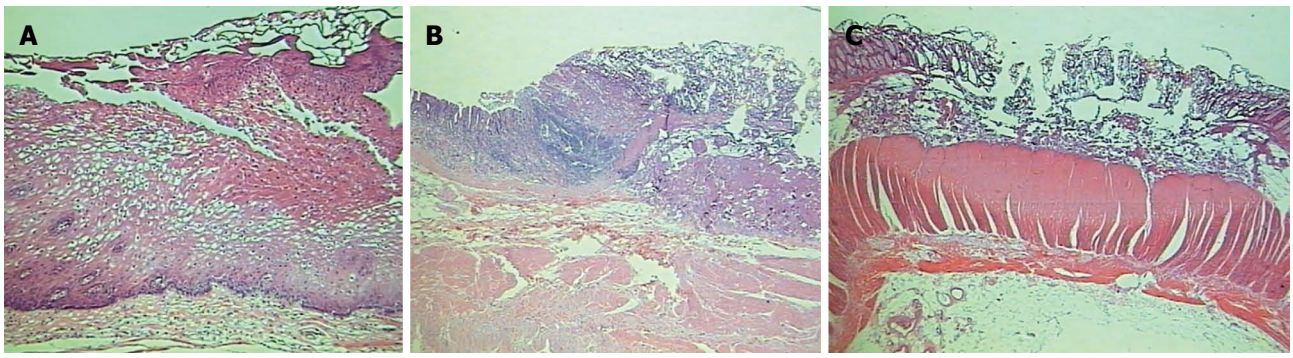

Figure 4 The microscopic aspect of coagulated spots with different depths of coagulation necrosis. A: Microscopic aspect of superficial mucosal involvement. Citoplasmatic acidofilia, cellular picnosis in an esophageal specimen [hematoxylin and eosin (HE), 250 ×]; B: Microscopic aspect of submucosal involvement in a gastric specimen (HE, 250 ×); C: Microscopic aspect of muscularis propria involvement in a colonic specimen (HE, 250 ×).

of the colon was less frequent when up to 70 W × 1 s was applied (27% to 45%). The same interval of energy caused involvement of the intermediate mucosa frequently (82% of the cases). These findings are relevant as stenosis of the colon, similar to the esophagus', usually are symptomatic. This consequence, however, can be minimized using lower amounts of energy, up to 70 J.

Damage of the muscularis propria of the colon occurred even when smaller amounts of energy were used. Although the frequency of this involvement was higher with bigger amounts of energy, reaching 45%, these findings alert to the care to be taken when APC is used in this organ, for the risk of perforation. Indeed, despite the use of a 40 W potency, Wahab *et al*[12] noticed one case of perforation in the cecum. Canard *et al*[22] used APC with 30 to 80 W to treat radiation proctitis and had three severe complications (extensive necrosis, perforation and hemorrhage), all of them when potency was above 45 W.

Vargo[8] reviewed eight papers (151 patients) dealing with the treatment of radiation proctitis with APC in potencies of 40 to 60 W. The incidence of success was high, independently of the power setting. In the other hand, major complications were observed in only three cases, a rectum-vaginal fistulae and two stenosis. These complications could be explained by the use of higher potencies, 50 W and 60 W, respectively. Our results differ from those written by Johanns *et al*[20], who noticed injury of the muscularis propria of the colon, similarly to the esophagus, only when 155 W for 10 s was applied. In their methodology, the authors report fibrosis and cellular picnosis below the coagulation zone. For us, these findings were considered cellular necrosis, justifying the deeper involvement observed here.

The application of bipolar electrocoagulation to esophageal specimens results in more frequent involvement of the intermediate mucosa (67% to 100%) when 100 J or more were used. Damage of the muscularis mucosa were less frequent (up to 44%) when 200 J or less were applied. Between 250 and 500 J this involvement was 67% to 78%. These findings suggest that the interval between 100 and 200 J may be best suited to ablation of the intermediate mucosa, especially in circumferential

lesions with risk of healing retraction. Bipolar electrocoagulation did not resulted in damage of the muscularis propria of the esophagus in this study encouraging its use in clinical practice. Indeed, stenosis and perforation after Barrett´s treatment was significantly less frequently reported with the application of this method.

Kovacs *et al*[23] observed 5% of stenosis with the use of bipolar electro-coagulation on metaplasic epithelium in esophagus. Sampliner *et al*[24] observed only one case of stenosis out of 72 patients treated the same way. Sharma *et al*[25] and Sampliner *et al*[26] had no complications. However success rates were also lower, 81%, 78% and 73%, respectively. Montes *et al*[27] were successful in 100% of their cases by applying bipolar electrical current, with power of 20 W, on Barrett's esophagus; unfortunately the study doesn't specified electrocoagulation time employed. Electrocoagulation with higher power settings and for longer time might optimize the results of this method for the treatment of Barrett´s esophagus, keeping a lower risk for complications when compared to argon plasma. In the other hand, using argon plasma one can cover extensive areas faster than with the use of bipolar coagulation justifying the popularity of the first method. To overcome this limitation, Ganz *et al*[28] published the application of a new electrocoagulation probe with an adjustable balloon that allows contact to the entire circumference of the organ. The device has been used in three patients before surgery for esophageal cancer. Electrocoagulation was performed with 260 to 350 W power settings for 0.8 s (energy density of 10 to 12 J/cm^2). There were no cases of perforation. A histological evaluation of these specimens showed mucosal ablation of 75% to 95% of the treated area in the two cases that the balloon contacted the whole circumference of the organ. The lamina propria was involved in all the three cases, being the muscularis mucosa totally involved in the majority of the coagulated areas. In a preliminary study using a porcine model (n = 12), electrocoagulation of healthy mucosa was performed with 350 W power setting and energy densities varying from 5 to 20 J/cm^2. The application of more than 12 J/cm^2 resulted in involvement of the submucosa and, above 15 J/cm^2; damage of the muscularis propria was seen. There was one case of peri-esophageal effusion when 20 J/cm^2 was used. This result is consistent with our findings, as, despite the ideal interval for these authors be 200 to 280 J, their target was the involvement of the muscularis mucosa. The concept of controlled deliverance of energy to the GI wall culminated with the introduction of radiofrequency ablation for the treatment of Barrett's esophagus. In radiofrequency sessions both the amount of energy and the contact of the balloon-based probe with the mucosal surface are controlled which seem critical to the good results achieved with this technique[29].

In this study, when bipolar electrocoagulation was used, the frequency of involvement of the intermediate mucosa of the stomach was low, up to 45%, except when the combination 20 W × 3 s was used, raising its involvement to 64%. Damage of the muscularis mucosa varied between 0 and 18% in all combinations of power setting and time except with the combination 20 W × 3 s, when it was 27%. This combination was the only one that presented damage to the muscularis propria, in only one coagulated point (9%). There was no correlation between power setting or time of application and involvement of the intermediate mucosa or muscularis mucosa of the stomach. These findings suggest that bipolar electrocoagulation of the stomach surface can be safely applied, even with higher power settings and longer time, as the risk of muscularis mucosa damage is low and muscularis propria very rare.

Although characteristic features of antral vascular ectasia are found in the lamina propria of the mucosa, the variants mentioned above could explain the therapeutic success of bipolar electrocoagulation in the treatment of this condition, like the results observed by Binmoeller *et al*[30] and Jensen *et al*[10].

Morris *et al*[31] studied the effect of this method to the gastric wall of dogs. The animals were maintained alive for the next seven days, when the depth of the wall involvement was analyzed. They observed deeper involvement, using similar combinations of power setting and time than we did. However some considerations can be pointed out. The thickness of the specimens wall was not described, not allowing comparison and, histological analyses took place one week after coagulation. It is not established if this interval is responsible for healing or increasing the thermal lesion.

In the colon, electrocoagulation with smaller amounts of energy, up to 60J (20 W × 3 s), caused injury of the muscularis mucosa less frequently (9% to 30%), while the interval between 100 and 500 J provoked this involvement in 55% to 82%. In the other hand, less frequent muscularis mucosa involvement with less chance of stenosis was obtained with amounts of energy that provoked less damage to the intermediate mucosa (55% to 64% of the cases-up to 60 J and 82% to 100% of involvement-150 to 500 J). When the method was applied for longer interval (10 s), the muscularis propria was involved in 9% to 10% of the coagulated points, similarly to Jensen´s *et al*[32] findings. Although this could be considered a low incidence, this involvement should be pointed out for the risk of perforation. The application for short intervals (up to 5 s), even with 50 W power setting, did not caused muscularis propria damage in any coagulated point, offering better safety for clinical practice.

We would also like to emphasize that in this study as in Jensen´s *et al*[32], cecum specimens, known for presenting a thinner wall, were not used. Application of any thermal method on this colon segment should be performed more cautiously. Radiation lesions are also special situations for being located in ischemic, less resistant tissue.

In this study, electrocoagulation appeared safer than argon plasma also in the colon. Causing a more superficial damage, it seems to be adequate to lesions such as

vascular ectasias. Nevertheless, Jensen *et al*[9] related one case of perforation after treating colonic vascular ectasias.

In conclusion, involvement of the intermediate mucosa of the stomach and of the muscularis mucosa of the stomach and the colon by argon plasma coagulation were more frequent when higher amounts of energy were used (above 90 J). The same tendency was observed in the esophagus samples for the involvement of the muscularis mucosa (above 150 J). In the esophagus and in the colon, injury of the intermediate mucosa caused by this method was frequent, even when small amount of energy was used (50 J). Injury of the muscularis propria was observed in 9% to 45% of the colon samples, depending on the amount of energy used. In the esophagus and in the stomach, the involvement of the muscularis propria was rare.

The use of bipolar electrocoagulation resulted in more frequent involvement of the intermediate mucosa and of the muscularis mucosa of the colon when higher amounts of energy were used (100 J or more). The same tendency was observed in the esophagus samples. In the stomach, the frequency of involvement of the intermediate mucosa and of the muscularis mucosa by the latter method was low, even when more energy was used (until 500 J). The risk of injury of the muscularis propria was low in the stomach and in the colon, not being observed in the esophagus.

Bipolar electrocoagulation seemed to cause more superficial injury to the specimens walls when compared to argon plasma coagulation, however the difference was statistically significant only for stomach specimens.

COMMENTS

Background

The association of diathermy to endoscopy has provided significant advances in endotherapy, which became a valuable alternative to traditional surgery and therapeutic procedure of choice in several conditions (*e.g.*, sphyncterotomy, polypectomy). The best way of applying heat to tissue has not been clearly established for hollow organs so far.

Research frontiers

The best way of applying heat to hollow digestive organs during thermal endoscopic therapy has not been clearly established so far. This study analyzes the histophathological effect of bipolar electrocoagulation and argon plasma coagulation on fresh surgical specimens of the digestive tract.

Innovations and breakthroughs

This study analyzes the histopathological effect of bipolar electrocoagulation and argon plasma coagulation on fresh surgical specimens of the digestive tract. Tissue damage after argon plasma coagulation is deeper than bipolar electrocoagulation. Both of them depend on the amount of energy used.

Applications

The use of argon plasma coagulation is popular in therapeutic endoscopy probably because it is easily available, has low cost, large surfaces of mucosa can be treated in one session and it causes allegedly superficial damage to the GI wall. These findings suggest that lower power settings are probably safer when argon plasma coagulation is employed at the colorectal and esophageal wall.

Terminology

Bipolar coagulation: the passage of electrosurgical current occurs within the accessory. Argon plasma coagulation: the passage of monopolar electrosurgical current occurs through a cloud of argon gas.

Peer review

This study deals with a topic that is very much valued by the endoscopic digestive surgeons, that is the laser argon versus the bipolar coagulator, which one the safer and more effective way of cauterization would be among them two.

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RETROSPECTIVE STUDY

Improved endoscopic retrograde cholangiopancreatography brush increases diagnostic yield of malignant biliary strictures

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Author contributions: All authors contributed equally to this work; Shieh FK, Khara HS, Shellenberger MJ, Johal AS and Diehl DL were involved in the clinical management, procedural performance and tissue acquisition of the cases; Luong-Player A, Liu H and Lin F were involved in the cytopathological analysis and diagnostic assessment of the cases.

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Abstract

AIM: To determine if a new brush design could improve the diagnostic yield of biliary stricture brushings.

METHODS: Retrospective chart review was performed of all endoscopic retrograde cholangiopancreatography procedures with malignant biliary stricture brushing between January 2008 and October 2012. A standard wire-guided cytology brush was used prior to protocol implementation in July 2011, after which, a new 9 French wire-guided cytology brush (Infinity sampling device, US Endoscopy, Mentor, OH) was used for all cases. All specimens were reviewed by blinded pathologists who determined whether the sample was positive or negative for malignancy. Cellular yield was quantified by describing the number of cell clusters seen.

RESULTS: Thirty-two new brush cases were compared to 46 historical controls. Twenty-five of 32 (78%) cases in the new brush group showed abnormal cellular findings consistent with malignancy as compared to 17 of 46 (37%) in the historical control group (P = 0.0003). There was also a significant increase in the average number of cell clusters of all sizes (21.1 *vs* 9.9 clusters, P = 0.0007) in the new brush group compared to historical controls.

CONCLUSION: The use of a new brush design for brush cytology of biliary strictures shows increased diagnostic accuracy, likely due to improved cellular yield, as evidenced by an increase in number of cellular clusters obtained.

Key words: Malignant biliary stricture; Endoscopic retrograde cholangiopancreatography; Brush cytology; Diagnostic yield; Cytopathology

Core tip: The sensitivity of brush cytology for biliary strictures has historically been low (around 30%-60%). Many studies have described efforts to improve cellular yield and diagnostic accuracy with varying success. We describe the development of an improved biliary brush cytology protocol with the use of a new biliary brush design which more than doubled the diagnostic yield of our brush cytology as compared to the historical cases. Cytopathological analysis also showed increased cellular yield, and thus better diagnostic accuracy, with the improved protocol implementation.

Shieh FK, Luong-Player A, Khara HS, Liu H, Lin F, Shellenberger MJ, Johal AS, Diehl DL. Improved endoscopic retrograde cholangiopancreatography brush increases diagnostic yield of malignant biliary strictures. *World J Gastrointest Endosc* 2014; 6(7): 312-317 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i7/312.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i7.312

INTRODUCTION

Brush cytology during endoscopic retrograde cholangiopancreatography (ERCP) remains one of the most common approaches to sample biliary strictures. Cytologic brushing has an excellent safety profile, widespread availability, and is relatively quick and simple to perform[1,2]. However, the reported sensitivity for brush cytology is low, ranging from 30%-60%[3]. Many studies have described efforts to improve cellular yield and diagnostic accuracy. These include disruption of the biliary epithelium by dilating the stricture prior to brushing, two or more brush passes, use of an extra-long cytology brush, immunohistochemistry, cell block method, and mutational analysis, all with varying success[4-15].

Obtaining adequate cellular yield appears to be a key factor in maximizing diagnostic sensitivity and accuracy. In 2011, a new wire-guided cytology brush (Infinity sampling device, US Endoscopy, Mentor, OH) was released for use. This brush has a 9 French sheath, and a combination of stiff and soft bristles designed with the objective of maximizing tissue acquisition. The aim of our study was to see if the use of this new brush would be able to improve the diagnostic sensitivity of ERCP-guided biliary brushing of malignant biliary strictures.

MATERIALS AND METHODS

Retrospective chart review of consecutive ERCPs, performed between January 2008 and October 2012 at our academic center, was conducted. ERCP procedures which involved cytologic brushing of a biliary stricture for suspected malignant biliary obstruction were included in the study. All patients were eventually diagnosed with a malignant biliary obstruction either by endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) or by surgical resection. Our study was approved by the Geisinger Health System Institutional Review Board.

Procedures performed between January 2008 and June 2011 served as historical controls. In this cohort, ERCP cytology brushing was performed with a standard 8 French wire-guided brush (Cytomax, Cook Medical, Bloomington IN; or RX, Boston Scientific, Marlborough MA). Two passes, each with multiple to-and-fro movements across the biliary stricture, were performed. Smears on slides were prepared, and the brush head was then cut off and sent in the cytology transport medium (RPMI).

A standardized protocol was instituted on July 1st, 2011 for ERCP brushing of biliary strictures. All cases were performed with the new 9 French wire-guided cytology brush (Infinity sampling device, US Endoscopy, Mentor, OH) (Figure 1). This brush can be used with a short wire as well as a long wire system. After placement of a biliary guidewire across the stricture, two separate passes, each with multiple to and fro movements, were performed with the brush across the biliary stricture. With the cytologic material collected from the first pass, two touch-prep smears were prepared, one of which was sprayed with fixative (Protocol Cytologic Fixative, Fisher Scientific, Pittsburgh, PA), and the other smear was air-dried. The brush was then agitated in the RPMI cytology fluid to dislodge accumulated cellular material. The brush was subsequently rinsed with water and a second pass was performed with the same brush over the biliary guidewire. The brush was then removed; the brush head was cut off and placed into the same tube of RPMI cytology fluid (Figure 2).

Figure 1 Detail of the 9 French cytology brush (Infinity sampling device, US Endoscopy, Mentor, OH).

Salvage cytology was performed by injecting 5 mL of RPMI cytology fluid through the brush catheter after brushing was completed. The two smear slides and the tube of RPMI containing the brush head and salvage cytology were all submitted to cytology. The smears were stained, and a cell block was made from the tube contents. Smears and cell blocks were reviewed by 2 experienced cytopathologists blinded to the final diagnosis. Cellular yield was meticulously quantified by counting the number and size of cell clusters seen (large clusters > 50 cells, medium clusters 6-49 cells, small clusters 2-5 cells, and single cells). In accordance to current standards in the literature, cytopathological diagnosis of "malignant" or "suspicious" were considered positive, while "atypical" cases were considered negative[9].

RESULTS

Thirty-two new protocol cases and 46 historical controls were analyzed. There were no significant differences in gender (63% *vs* 56% male, respectively, $P = 0.55$), or age (mean 70 *vs* 68 years old, respectively, $P = 0.45$) between the groups. The majority of cases were either pancreatic adenocarcinoma or cholangiocarcinoma as eventually confirmed by EUS-FNA or surgical resection. The degree of the biliary strictures was similar in both

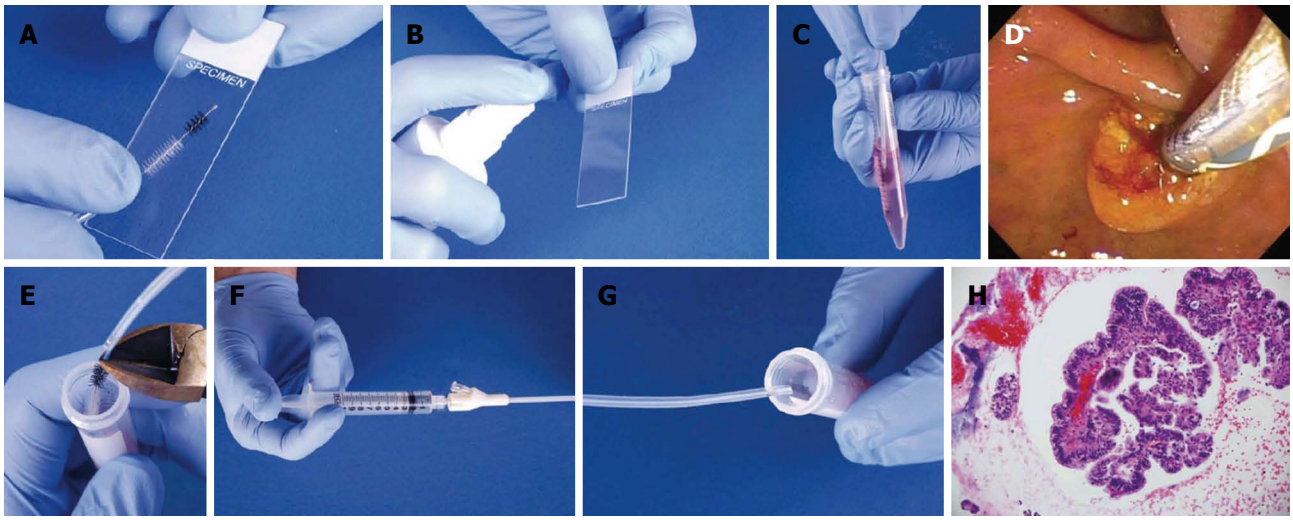

Figure 2 Brushing technique. Two passes performed in the stricture. A, B: The first pass was used to make two smears (A), with one smear sprayed with fixative (B); C: The brush was then agitated in the RPMI cytology fluid to dislodge material into the fluid; D: The brush was rinsed with water. A second pass was performed with the same brush; E: The brush was cut off into the same tube of RPMI; F, G: Contents of catheter were flushed *via* salvage cytology technique; H: The sample was processed as a cell block.

Table 1 Diagnostic yield for the new brush protocol *vs* historical control

	New brush protocol	Historical control	*P* value
Mean age (yr)	70	68	0.45
Gender (males)	63%	56%	0.55
All cases	25/32 (78%)	17/46 (37%)	0.0003
Pancreatic adenocarcinoma	17/23 (74%)	6/20 (30%)	0.005
Cholangiocarcinoma	7/7 (100%)	8/22 (36%)	0.004
Other	1/2 (50%)	3/4 (75%)	0.6
	2 gallbladder cancers	2 gallbladder, 1 colon, 1 unknown	

the groups. The 32 cases in the new protocol cohort consisted of 23 cases of pancreatic adenocarcinoma, 7 cases of cholangiocarcinoma, and 2 gallbladder cancers. Twenty-five of these 32 (78%) cases were diagnosed with malignancy based on biliary brush cytology using the new brush and cytology protocol. The 46 cases in the historical control group consisted of 22 cases of cholangiocarcinoma, 20 cases of pancreatic adenocarcinoma, and 4 others (2 gallbladder cancers, 1 colon cancer, 1 of unknown primary). Seventeen of these 46 (37%) cases were diagnosed with malignancy based on biliary brush cytology using the standard brushes and cytology yield. There was an increased diagnostic yield of brush cytology of these malignant biliary strictures in the new protocol group as compared to the historical controls (P = 0.0003) (Table 1).

There was also a significant increase in the average number of cell clusters of all sizes obtained with the new brush compared to the standard brushes (21.1 *vs* 9.9 clusters, P = 0.0007). This relationship held true when cluster size was broken down into four different categories (large clusters > 50 cells, medium clusters 6-49 cells, small clusters 2-5 cells, and single cells) for all cases. For each of

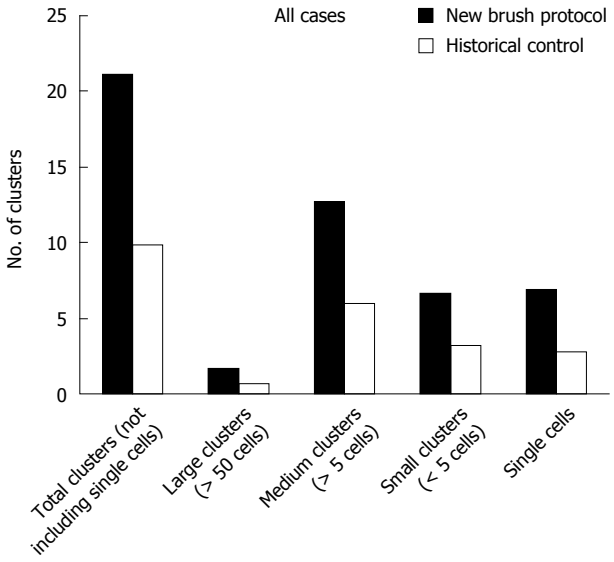

Figure 3 Number of clusters obtained by cytologic brushing for all cases.

the subsets of cluster size, there was a significant increase in the number of clusters in the new brush group compared to the historical control group (P = 0.005, 0.0004, 0.01, 0.009 respectively) (Figure 3).

In the subgroup of patients with pancreatic adenocarcinoma, there was an increase in average total cell clusters of all sizes (20.9 *vs* 6.1, P = 0.001) as well as large, medium, small clusters and single cells (P = 0.0001, 0.0001, 0.0004, and 0.0012, respectively). Diagnostic yield was 74% (17/23) in the new brush group compared to 30% (6/20) in the historical controls, P = 0.005.

Similar results were seen in the subgroup of patients with cholangiocarcinoma, with an increase in average total cell clusters of all sizes (24.6 *vs* 10.8), as well as large, medium, small clusters and single cells (P = 0.04, 0.01, 0.03, and 0.01, respectively). Diagnostic yield was 100%

(7/7) for the new brush group compared to 36% (8/22) in the historical controls, $P = 0.004$.

DISCUSSION

Tissue diagnosis of biliary strictures is of critical importance in treatment planning. This is usually done *via* brush cytology during ERCP, however the diagnostic yield with standard brushings have been low and variable. Changes in technique (predilation, making a second pass, or scraping the stricture with the tip of the cytology brush catheter) can increase yield. Forceps biopsy at the time of ERCP can also be done, with slightly higher diagnostic yield (43%-60%)[3], but can be technically challenging to obtain in some certain cases, especially by less experienced endoscopists. In addition, the diagnostic yield can be low in extrinsic biliary obstruction such as from pancreatic head cancer as compared to cholangiocarcinoma, which typically has an intraductal lesion.

Per-oral cholangioscopy can have sensitivities as high as 78%-89% for the diagnosis of malignancy in indeterminate biliary strictures. However, the utility of this method is limited due several reasons such as scope fragility, requirement of special equipment with high acquisition costs, and requirement of a high level of endoscopic expertise. In addition, "real world" results have not matched those initially obtained by a group of highly skilled biliary endoscopists. Furthermore, tissue sampling is still required for a diagnosis of malignancy which is usually performed through either brush or biopsy methods[6,16,17].

Endoscopic ultrasound allows detailed examination of the common bile duct and pancreatic head, and tissue sampling can be performed *via* EUS-FNA with diagnostic yield as high as 89%[12,18-21]. However, many patients who undergo EUS-FNA for the diagnosis of ductal malignancy will have already undergone ERCP with brushing, and there are costs associated with the second procedure. If EUS-FNA is done in cases of cholangiocarcinoma, there is the potential for tumor seeding. In fact, the Mayo Clinic protocol for liver transplantation in cholangiocarcinoma considers FNA to be a contraindication to liver transplantation[12,22,23]. Probe-based confocal laser endomicroscopy is a newer technology which can offer real-time histologic evaluation of indeterminate biliary strictures during ERCP with overall diagnostic accuracy of over 80%, but it is not widely available, and further studies need to be performed prior to more generalized use[24-28].

A potentially unrecognized source of variability in sampling is how specimens are handled after they are obtained. Some endoscopists always make a smear, and some never do. Some cytology departments always make a cell block and some do this only on request. There is evidence that creation of a cell block can increase the cellular yield and ability to interpret architecture, thereby increasing the sensitivity of cytodiagnosis compared to conventional smears[15]. Multiple studies have consistently shown that cell block along with smear cytology can markedly improve both the sensitivity and specificity of cytologic specimens in the diagnosis of malignancies, especially when the diagnosis from smear alone is non-diagnostic, and that it is cost-effective[29-34]. The increased quantitative cytology yield is also useful if more specialized tests are required on the tissue. For example, detection of aneuploidy *via* digital image analysis (DIA) or fluorescence in situ hybridization (FISH) may be useful in increasing the diagnostic yield in certain difficult indeterminate biliary strictures[35].

Several aspects of the new brush design are likely to have contributed to improved results. The new brush incorporates an increased brush diameter and length, as well as a new bristle design. Stiffer bristles are present on the proximal and distal ends of the brush, which may dislodge more underlying tissue due to a more abrasive effect. Softer bristles in the middle of the brush are then able to capture the abraded material. Some authors recommend removing the brush and catheter as a unit, to prevent loss of cellular material[5]. The new brush also has a slightly larger catheter (9 French compared to 8 French) which decreases the "squeegee effect" of causing tissue loss from the bristles when the brush is retracted. This slightly bigger catheter size did not cause any technical difficulties in advancing the brush over the biliary wire to the desired location as compared to the 8 French brushes. The ability to collect cells for so-called "salvage cytology" from the brush sheath may also contribute to the increase in the amount of tissue collected[36,37]. It is logical that more tissue disruption prior by brushing can improve cellular yield; which is supported by studies demonstrating that two consecutive brushings improved cancer detection rate from 33% to 44%[7], and three consecutive brushings increased the rate from 40% to 60%[38]. In the new brush protocol, we uniformly performed two passes, which may also have contributed to the better diagnostic yield. One limitation of our study is that it is a retrospective review, and the new brush was used in conjunction with a standardized brushing and specimen processing protocol, which may potentially affect the outcomes of the results. However, other than the brush design itself, the tissue acquisition and processing technique was similar in both groups.

With the use of a newly designed ERCP cytology brush, we were able to more than double the diagnostic yield of our brush cytology. Proper specimen processing with the production of smears as well as cell-blocks further increases the cytologist's ability to make a firm diagnosis on the obtained tissue. When it comes to the pathologist's point of view, "tissue is the issue" and increased tissue yields improves the pathologist's ability to make a diagnosis in cases of potentially malignant biliary stricture.

ACKNOWLEDGMENTS

Data from this study was presented in May 2013 as a

poster presentation at Digestive Disease Week 2013 in Orlando, FL, United States.

COMMENTS

Background

The sensitivity of brush cytology for biliary strictures during endoscopic retrograde cholangiopancreatography has historically been low (around 30%-60%) despite various technical variations.

Research frontiers

There is a great need to improve the diagnostic yield of biliary brushings, which is most common and widely used modality for evaluation of biliary strictures.

Innovations and breakthroughs

Many studies have described efforts to improve cellular yield and diagnostic accuracy. These include disruption of the biliary epithelium by dilating the stricture prior to brushing, two or more brush passes, use of an extra-long cytology brush, forceps biopsy method, per-oral cholangioscopy, endoscopic ultrasound-guided fine needle aspiration, probe-based confocal laser endomicroscopy, immunohistochemistry, cell block method, fluorescence *in situ* hybridization and mutational analysis, all with varying success.

Applications

The goal was to determine if by simply using a new brush design and implementing a standardized cytology processing protocol would improve the diagnostic yield of biliary stricture brushings as compared to historical controls.

Peer review

This is a well-written manuscript dealing with an interesting topic. The methodology is straight-forward and the conclusions drawn are in concern with the logics and results of the study.

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RETROSPECTIVE STUDY

Conservative approach in Peutz-Jeghers syndrome: Single-balloon enteroscopy and small bowel polypectomy

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Abstract

AIM: To assess the usefulness of the balloon assisted enteroscopy in preventing surgical intervention in patients with Peutz-Jeghers syndrome (PJS) having a small bowel large polyps.

METHODS: Seven consecutive asymptomatic pts (age 15-38 years) with PJS have been collected; six underwent polypectomy using single balloon enteroscopy (Olympus SIF Q180) with antegrade approach using push and pull technique. SBE system consists of the SIF-Q180 enteroscope, an overtube balloon control unit (OBCU Olympus Balloon Control Unit) and a disposable silicone splinting tube with balloon (ST-SB1). All procedures were performed under general anesthesia. Previously all pts received wireless capsule endoscopy (WCE). Prophylactic polypectomy was reserved mainly in pts who had polyps > 15 mm in diameter. The balloon is inflated and deflated by a balloon control unit with a safety pressure setting range from -6.0 kPa to +5.4 kPa. Informed consent has been obtained from pts or parents for each procedure.

RESULTS: Six pts underwent polypectomy of small bowel polyps; in 5 pts a large polyp > 15 mm (range 20-50 mm in diameter) was resected; in 1 patient with WCE negative, SBE was performed for previous surgical resection of gastrointestinal stromal tumors. In 2 pts endoscopic clips were placed due to a polypectomy. No surgical complication have been reported. SBE with resection of small bowel large polyps in PJS pts was useful to avoid gastrointestinal bleeding and emergency laparotomy due to intestinal intussusceptions. No gastrointestinal tumors were found in subsequent enteroscopic surveillance in all seven pts. In order surveillance, all pts received WCE, upper endoscopy, ileocolonoscopy every 2 years. No pts had extraintestinal malignant lesions. SBE was performed when WCE was positive for significant polyps (> 15 mm).

CONCLUSION: The effective of prophylactic polypectomy of small bowel large polyps (> 15 mm) could be the first line treatment for conservative approach in management of PJS patients.

Key words: Peutz-Jeghers syndrome; Balloon assisted enteroscopy; Polypectomy

Core tip: Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by mucocutaneus pigmentation and multiple polyps in small bowel. Most of pts need surgical intervention for intussusceptions and gastrointestinal bleeding; the surgical risk is up to 50% in pts having a large polyps > 15 mm or rapidly growing. Enteroscopy balloon assisted with resection of

small bowel large polyps is useful to avoid emergency laparotomy after performing wireless capsule endoscopy. The effective of prophylactic polypectomy of small bowel large polyps could be the first line treatment for conservative approach in management of PJS patients.

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INTRODUCTION

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant hereditary disease due to mutation in serine/threonine kinase 11 tumour suppressor gene (STK 11 or LKB1), located on chromosome 19p13.3. The estimated incidence of PJS ranges between 1 in 50000 and 1 in 200000 live births[1]; it is characterized by mucocutaneous melanin pigmentation and hamartomatous polyps in the gastrointestinal tract[2]. These polyps are predominant in the small intestine (prevalence 64%), usually in the jejunum, followed by stomach and colon. The size of polyps requiring endoscopy resection for the high risk of intussusceptions, bleeding, obstruction and malignant transformation, has been considered > 15-20 mm in patients with polyposis[3]. However, the most frequent complication of PJS which occurred during the first decade of life, is intussusception that often needs multiple laparotomies with intestinal enterotomy that increase the risk for short-gut syndrome[4,5]. In the last few years, different diagnostic techniques have been developed for the assessment and therapeutic approach of small bowel polyps, such as small bowel follow-through, wireless capsule endoscopy (WCE), enteroclysis, magnetic resonance and balloon assisted enteroscopy (BAE). PJS is one of the most significant disease that benefit from WCE and BAE for management of this intestinal pathology. The diagnostic yield of WCE has been studied in PJS; usually it is safe, well tolerated and important for the detection of small bowel polyps smaller than 5 mm. When large polyps (> 15 mm) are detected, endoscopic intervention may be required to remove them. BAE is successfully used for surveillance and treatment in patients with PJS[6]. Since 2009, in our Istitution we are using single balloon enteroscopy (SBE) in pts with PJS for radical polypectomy that could provide a means of prophylactic polypectomy to prevent complications and avoid the need for laparotomy.

MATERIALS AND METHODS

Since 2009, we collected seven consecutive asymptomatic PJS pts (4 male, 3 female; age 15-38 years, mean age 22.2 years; weight 50-72 kg) underwent SBE (Olympus SIF Q180 enteroscope Olympus Optical Co., Tokyo, Japan) with anterograde approach and push and pull technique. Clinical and endoscopic characteristics of pts are summarized in Table 1.

Before SBE procedure, all pts received upper endoscopy, ileo-colonoscopy and WCE (GIVEN Imaging Ltd., Yoqneam, Israel) to detect polyps' location and size. WCE allows only an approximate estimation of the size of polyps based on previous experience, however, we estimated polyps size according to small bowel lumen size. The location of small-bowel polyps was estimated by analyzing the WCE transit time between pylorus passage and ileocecal valve. Prophylactic polypectomy was reserved mainly in patients who had polyps > 15 mm in diameter. SBE system consists of the SIF-Q180 enteroscope, an overtube balloon control unit (OBCU Olympus Balloon Control Unit) and a disposable silicone splinting tube with balloon (ST-SB1). The balloon is inflated and deflated by a balloon control unit with a safety pressure setting range from -6.0 kPa to +5.4 kPa. All procedures were performed under general anesthesia. Informed consent has been obtained from pts or parents for each procedure. Peroral insertion required the patient fast for 12 h. Perrectal insertion was not necessary because location of large polyps was predominantly in jejunum and proximal ileum. We performed polypectomy with a polypectomy snare and removed the excised polyp for histological evaluation. Polypectomy was carried out with ENDO CUT Q, a monopolar high frequency electrosurgical technique, based on cutting and coagulation cycles. All pts received intraoperative antibiotic prophylaxis. Fluoroscopic guidance was used when necessary to verify the correct looping and the withdrawal maneuvers of the endoscope. No hemoclips on the polyp pedicle prior to the polypectomy was placed to avoid post polypectomy bleeding. WCE and BAE were performed approximately every 2 years for surveillance and treatment of polyps. All pts underwent abdominal and testicular ultrasonography to exclude malignant extraintestinal complications. Ethical approval for this study was obtained from our ethics board.

RESULTS

Six pts underwent polypectomy of small bowel polyps; in these pts polyps were located in jejunum and proximal ileum according to WCE investigation previously performed (Figure 1). Five pts underwent to extensive polypectomy of small bowel large polyps > 15 mm in diameter (20 mm until 50 mm) (Figure 2); from three to five small bowel large polyps were removed in 5 pts. In one case WCE was normal; this patient underwent SBE for previous surgical resection for gastrointestinal stromal tumors (GIST); SBE was normal. Histological evaluation showed hamartoma tissue in all polyps retrieved. No bleeding or surgical complications have been reported; no complications due to SBE occurred after procedures. In 2 pts endoscopic clips have been placed on a large tearing of intestinal mucosa due to polypectomy procedure (Figure

Table 1 Patient characteristics

Patients	Sex	Age (yr)	Previous surgery	WCE	SBE	No. of polyps removed in small bowel	Size of polyps (mm)	Histology
1	M	35	Intussusceptions	Jejunal large polyps	Proximal jejunal polyps	5	40	Hamartomatous polyps
2	M	34	Intussusceptions	Jejunal polyps	Proximal jejunal polyps	3	10	Hamartomatous polyps
3	F	16	Intussusceptions	Jejunal large polyps	Distal jejunal polyps	4	20	Hamartomatous polyps
4	F	21	Intussusceptions Laparotomy for perforation following colonic polyp	Jejunal large polyps	Proximal jejunal polyps	5	50	Hamartomatous polyps
5	M	31	Intussusceptions Lapatotomy for GIST	Normal	Normal (Biopsies)	-	-	Normal
6	M	17	Intussusceptions	Jejunal large polyps	Proximal jejunal polyps	4	40	Hamartomatous polyps
7	F	16	Intussusceptions	Jejunal large polyps	Proximal jejunal polyps	3	50	Hamartomatous polyps

GIST: Gastrointestinal stromal tumors; WCE: Wireless capsule endoscopy; SBE: Single balloon enteroscopy.

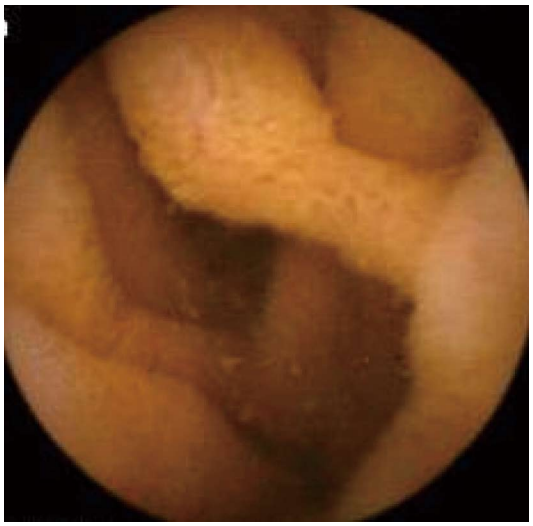

Figure 1 Wireless capsule endoscopy: Jejunal polyp.

3). Three of seven pts had multiple gastric micro polyps; no polypectomy was done. Four pts had multiple sessile colonic polyps, one of them with large multiple polyps underwent polypectomy. The mean procedure time was 72 min (range 60-120 min). Mean time of discharge of pts was 2 d. All pts had previous surgical resections of small bowel for polyps due to obstruction or intussusceptions. No gastrointestinal tumors were found in subsequent enteroscopic surveillance in all seven pts. All pts received WCE, upper endoscopy, ileocolonoscopy every 2 years. No pts had extraintestinal malignant lesions. SBE was performed when WCE was positive for significant polyps (> 15 mm).

DISCUSSION

PJS is characterized by hamartomatous polyps of small bowel predominantly located in the proximal jejunum. The majority of patients with PJS had a history of small bowel surgery. The risk of intussusception and intestinal obstruction before the age of 20 years is up to 50% in particular in patients having a large polyps > 15 mm or rapidly growing[6-8]. In the last few decades, several advanced endoscopic technique have been developed to allow a visualization of small bowel and therapeutic approach without surgery. Before the introduction of BAE, small bowel polyps were removed only by intraoperative endoscopy or surgical resection; now with BAE[9] it is possible to remove proximal end distal small bowel polyps endoscopically, preventing abdominal surgery. WCE and SBE play an important role in surveillance of patients affected by PJS. WCE is safe, well tolerated and permits to detect size, aspect and location of polyps on the entire length of the digestive tube[10,11]. In our series, all patients received upper endoscopy, ileocolonoscopy and WCE to detect polyps' location and size before SBE procedure. WCE allows only an approximate estimation of the size of polyps; therefore, based on previous experience, we estimated polyps size according to small bowel lumen size. Katsinelos *et al*[12] estimated size polyps as small or large, using an open pylorus orifice (diameter 10 mm) as a reference for polyp size estimation. BAE offers diagnostic and therapeutic options for small bowel surveillance in PJS patients[9]; it is a safe procedure also in patients with previously abdominal surgery and in children[13,14]. When significant polyps are detected (> 15 mm), BAE should be the preferred method for prophylactic polypectomy[15]; Sakamoto *et al*[3] reported no intussusceptions developed in all pts underwent small bowel polypectomy. In our experience, endoscopic resection of small bowel large polyps was important to reduce the risk of acute intestinal intussusceptions or obstruction in all seven pts; no patients underwent small bowel resection during the surveillance. Small bowel surveillance is recommended every 2-3 years for pts with PJS from the age of 8-10 years by WCE[16] and endoscopy; removal of significant small bowel polyps reduces emergency surgery[15-17]. Our surveillance program provide a screen-

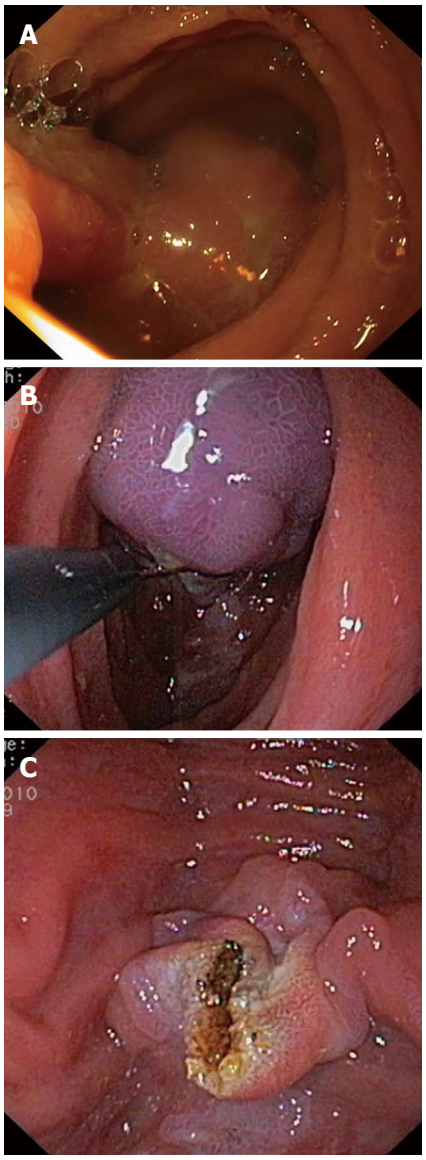

Figure 2 Extensive polypectomy of small bowel large polyps > 15 mm of diameter. A: Large jejunal polyp; B: Polypectomy: polyp captured with snare; C: Polyps pedicle post-polypectomy.

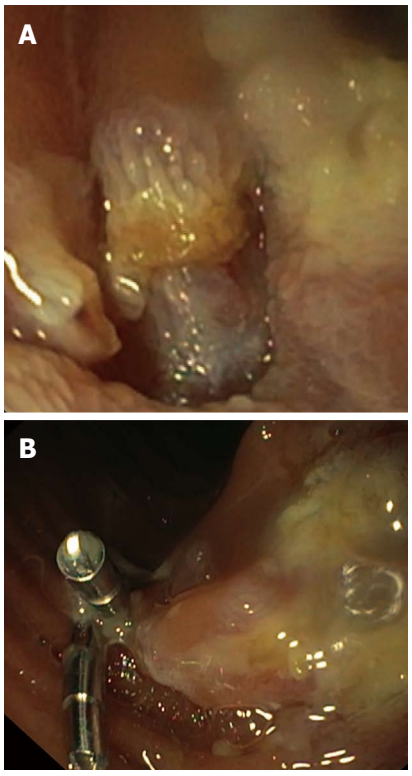

Figure 3 Endoscopic photograph. A: Tearing of intestinal mucosa post-polypectomy; B: Hemoclip placement.

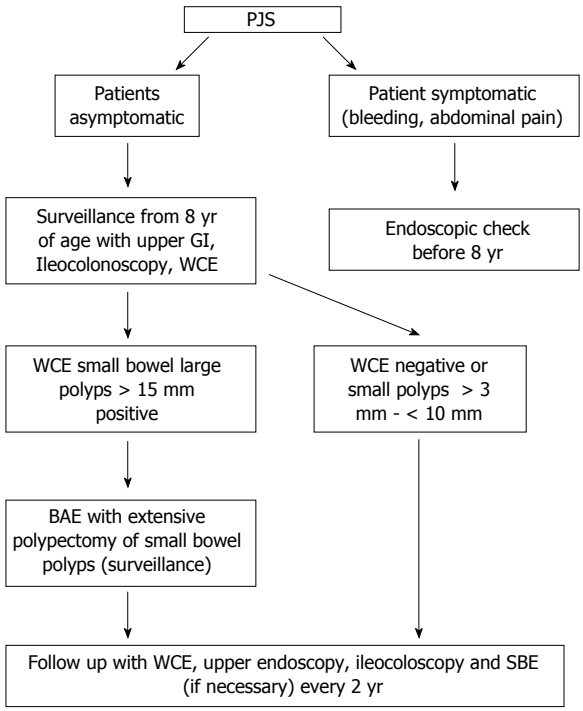

Figure 4 Surveillance algorithm. PJS: Peutz-Jeghers syndrome; WCE: Wireless capsule endoscopy; BAE: Balloon assisted enteroscopy; SBE: Single balloon enteroscopy. GI: Gastrointestinal.

ing from 8 years or earlier if symptomatic (bleeding, abdominal pain) with upper endoscopy, colonoscopy, WCE and SBE according to WCE polyps detection. We suggest elective polypectomy with SBE when significant small bowel polyps are detected (> 15 mm) and laparotomy when polypectomy is not possible (size of polyps > 5 cm or high risk of complications). Follow up with WCE, upper endoscopy and SBE, if necessary, is recommended every 2 years in asymptomatic pts (Figure 4). Cancer predisposition in patient with PJS is known; the risk involves the small bowel, stomach, colon, pancreas and extraintestinal organs as Sertoli cells, breast and ovary. Intestinal polyps can transform in cancer; the risk is related to their dimension, even if malignant transformation is found occasionally in PJS polyps; however transformation sequence hamartoma-adenoma-carcinoma has been described[18-20]. It seems that there is no risk of tumor for the polyps smaller than one centimeter in patients with PJS[9]. No gastrointestinal tumor was found in our patients series during follow-up. In the

past, one of our patients underwent surgical small bowel resection for gastrointestinal tumor, classified as a GIST at surgical specimen examination. Endoscopic polypectomy is a standardized technique and is not without risk. The hemoclip placement can be requested immediately after polyp resection[21,22]; in one of our cases hemoclip was used to avoid a post polypectomy complication due to a large tearing of small bowel mucosa. No bleeding and surgical complications have been reported after SBE procedure in our patients.

In a conclusion, PJS is a pathological condition that require a regular follow-up and screening during the life[23,24]; WCE and SBE procedures with resection of small bowel significant polyps are useful in asymptomatic patients to avoid severe gastrointestinal bleeding and emergency laparotomy due to intussusceptions[25]. About this, we reported our surveillance program that could be useful to follow-up patients affected by PJS. The effective of prophylactic polypectomy of small bowel large polyps could be the first line treatment for conservative approach in management of PJS patients.

COMMENTS

Background

The major problems in the management of Peutz-Jeghers syndrome (PJS) are a large small-bowel polyps, which can cause intussusception and bleeding. The most of pediatric patients with PJS undergo a laparotomy for an episode of intestinal obstruction before they reached 18 years of age and a second laparotomy within 5 years. Balloon assisted enteroscopy (BAE) and wireless capsule endoscopy (WCE) play an important role for diagnostic, care and screening of a large small bowel polyps. Cancer predisposition in patient with PJS is known; transformation sequence hamartoma-adenoma-carcinoma has been described. Surveillance protocols in PJS have two main purposes: one is to detect sizeable gastroenterological polyps which could cause intussusception/obstruction or bleeding/anaemia, second is the detection of cancer at an early stage.

Research frontiers

The need for endoscopic access to improve diagnosis and treatment of small bowel disease has led to the development of novel technologies one of which is non-invasive, the video capsule, and a type of invasive technique, the device-assisted enteroscopy. Before the introduction of BAE, small bowel polyps were removed only by intraoperative endoscopy or surgical resection; now with BAE it is possible to remove proximal end distal small bowel polyps endoscopically, preventing abdominal surgery. Also WCE is a useful examination for the supervision of small intestinal polyposis and PJS; BAE and WCE are complementary investigations in the assessment of small bowel diseases that led to a radical change in their management.

Innovations and breakthroughs

The authors described a method to avoid the risk of surgery using a conservative approach proposing a surveillance algorithm in the management of patient with PJS. Surveillance program provides a screening from 8 years in asymptomatic pts or earlier (before 8 years) if symptomatic with upper endoscopy, colonoscopy, WCE and SBE according to WCE polyps detection. We suggest elective polypectomy with SBE when significant small bowel polyps are detected (> 15 mm) and laparotomy when polypectomy is not possible (size of polyps > 5 cm or high risk of complications).

Applications

The manuscript suggests that it is possible to manage PJS patients using a conservative approach with single balloon enteroscopy (SBE) and capsule endoscopy investigations. This technique should be used in dedicated pediatric endoscopy centers.

Terminology

BAE is a procedure which can allow advancement of long endoscope (200 cm) into the small bowel for diagnostic and therapeutic purposes. BAE uses one or two balloon systems. The system using two balloons is called double balloon enteroscopy and the system using a single balloon is called SBE.The procedure can be performed via the upper gastrointestinal (GI) tract (antegrade) or through the lower GI tract (retrograde).

Peer review

This study describes a safe and useful technique for treatment of small bowel large polyps in patients with polyposis syndrome. The application of the balloon assisted enteroscopy may avoid surgical intervention in patients with Peutz-Jeghers syndrome. It is well written.

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CASE REPORT

Endoscopic and imaging appearance after injection of an ano-rectal bulking agent

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Abstract

The use of hyaluronic acid and dextranomer (Solesta, Salix) injection in the anal canal is an emerging modality in the treatment of fecal incontinence. However, little is known regarding the endoscopic and radiological appearance following injection of this ano-rectal bulking agent. We report computed tomography and endoscopic findings after hyaluronic acid/dextranomer injection in the ano-rectal area.

Key words: Fecal incontinence; Ano-rectal bulking agent; Hyaluronic acid; Dextranomer

Core tip: The use of hyaluronic acid and dextranomer (Solesta, Salix) injection in the ano-rectum is an emerging modality in the treatment of fecal incontinence. Our case discusses the endoscopic and radiological findings after injection of this bulking agent in the ano-rectal area.

Papafragkakis H, Changela K, Bhatia T, Ona MA, Malieckal A, Paleti V, Fuksbrumer MS, Anand S. Endoscopic and imaging appearance after injection of an ano-rectal bulking agent. *World J Gastrointest Endosc* 2014; 6(7): 324-327 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i7/324.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i7.324

INTRODUCTION

Fecal incontinence (FI) is defined as the involuntary loss of liquid or solid stool for more than one month. The prevalence of FI ranges between 1.6% and 15%[1,2]. FI is an underdiagnosed condition that may cause psychosocial stigma and poses a clinical challenge to treat. The use of hyaluronic acid and dextranomer (Solesta, Salix) injection in the anal canal is an emerging modality in the treatment of fecal incontinence. However, little is known regarding the endoscopic and radiological appearance following injection of this ano-rectal bulking agent.

CASE REPORT

An 89-years-old woman underwent injection of hyaluronic acid/dextranomer in the anal canal for fecal incontinence under endoscopic guidance (Figure 1). Two days later, the patient had computed tomography (CT) scan of the abdomen and pelvis, which showed mural rectal thickening with multiple round hypodense foci within the rectal wall (Figure 2). Mucinous mural adenocarcinoma and abscess were among the radiological differential diagnosis.

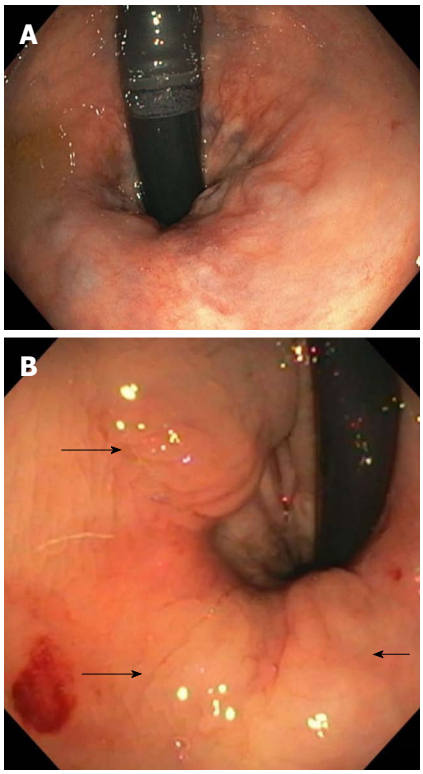

Figure 1 Endoscopic view. A: Endoscopic view of anal canal before hyaluronic acid/dextranomer (Solesta, Salix) injection; B: Endoscopic view of post-hyaluronic acid dextranomer (Solesta, Salix) injection showing the submucosal bulking property of the agent (black arrows).

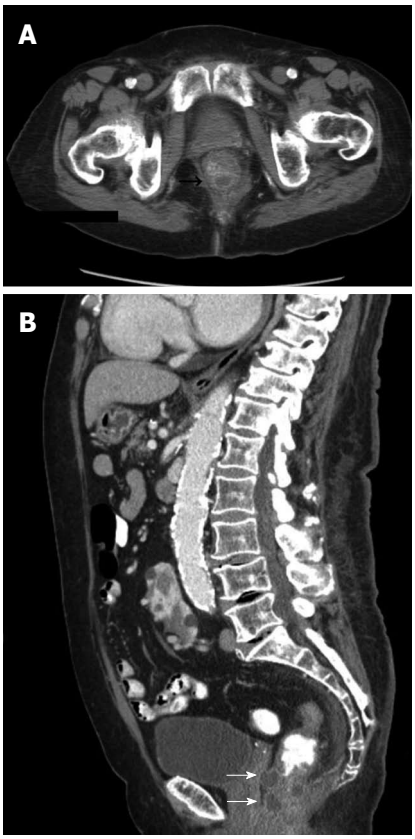

Figure 2 Computed tomography scan. A: Computed tomography scan axial view showing mural thickening with multiple rounded hypodense foci within the posterior rectal wall; B: Computed tomography scan sagittal view showing multiple rounded foci within the anterior and posterior rectal wall (white arrows).

DISCUSSION

We report a case of CT and endoscopic findings after hyaluronic acid/dextranomer injection in the ano-rectal area.

Current treatment options for FI include conservative measures, medications and surgery. Conservative approaches include pelvic floor muscle training, diet modifications, use of pads or plugs and biofeedback[3-5]. Biofeedback, assisted by a therapist and using electrodes placed on the abdomen and in the rectum, can help patients gain control of the pelvic musculature and improve FI symptoms. A study by Lacima *et al*[6] demonstrated that the majority of patients managed with biofeedback achieved 75% reduction in incontinence episodes or fully recovered compared to controls.

Medical management of FI commonly begins with antidiarrheals, such as loperamide, although their use is often limited by the development of constipation[7]. Amitriptyline, a tricyclic antidepressant, is also used for the management of FI, however, with modest efficacy[8]. Clonidine, a centrally acting α_2 adrenergic agonist, has been demonstrated to reduce symptoms and increase incontinence-free days in women with predominantly urge-related fecal incontinence[9].

Invasive interventions are currently the last resort for the management of FI. They include sacral nerve stimulation, radiofrequency treatment and surgery. The exact mechanism of action of sacral nerve stimulators is not fully understood, but it is thought to be related to improved ano-rectal angulation and amplification of anal closing pressures[10]. Radiofrequency treatment causes a topical burn with subsequent remodeling and tightening of the ano-rectal muscles and has shown conflicting results in the management of FI[11]. More studies are needed to establish the efficacy and application of this treatment modality. Surgery remains the last resort for refractory FI. The long term results after sphincter repair are modest[12-14]. In patients with internal rectal prolapse, anterior rectopexy may be promising as an alternative surgical approach[15]. The use of an artificial anal sphincter or a magnetic anal sphincter are other novel surgical approaches, but more studies are needed to establish their use[16].

The use of hyaluronic acid/dextranomer (Solesta, Salix), a non-allergenic, biocompatible bulking agent, which causes a tissue-like formation in the anal canal can provide an alternative to surgical treatment when conservative management has failed. Hyaluronic acid/dextranomer (Solesta, Salix) applied through transanal submucosal injection provides support for the ingrowth of fibroblasts and collagen[17]. The 12-mo efficacy and safety of this ano-rectal bulking agent has been demonstrated in trials[10,18]. A recent study by La Torre *et al*[19] demonstrated the efficacy and durability of a hyaluronic acid/dextrano-

mer agent 24 mo after use. Almost 63% of the patients demonstrated good response and had more than 50% reduction of incontinence episodes 24 mo after injection.

Hyaluronic acid/dextranomer application is increasing as more physicians are aware of its efficacy in the management of FI. However, little is known regarding the radiological and endoscopic appearance after its use. As demonstrated in our report, the CT findings may show mural rectal thickening with hypodense foci within the ano-rectal wall, which may mimic abscess or tumor. There have been anecdotal reports of surgical removal of ano-rectal bulking agent implants due to confusion about its appearance. These changes are likely permanent and therefore, it is important for gastroenterologists, surgeons and radiologists to be cognizant of the endoscopic and radiological appearance of the ano-rectum after hyaluronic acid/dextranomer injection and inquire about previous bulking agent injection in that area.

COMMENTS

Case characteristics

An 89-years-old woman underwent injection of hyaluronic acid/dextranomer in the anal canal for fecal incontinence under endoscopic guidance.

Clinical diagnosis

Fecal incontinence.

Differential diagnosis

Mucinous mural adenocarcinoma, abscess.

Imaging diagnosis

Computed tomography (CT) scan axial view showed mural thickening with multiple rounded hypodense foci within the posterior rectal wall. CT scan sagittal view showed multiple rounded foci within the anterior and posterior rectal wall. Endoscopic view of post-hyaluronic acid/dextranomer (Solesta, Salix) injection showed the submucosal bulking property of the agent.

Treatment

Submucosal injection of hyaluronic acid/dextranomer (Solesta, Salix) into the ano-rectum.

Related reports

Little is known regarding the endoscopic and radiological appearance following injection of this ano-rectal bulking agent.

Term explanation

Hyaluronic acid/dextranomer (Solesta, Salix) is a non-allergenic, biocompatible bulking agent, which causes a tissue-like formation in the anal canal that can provide an alternative to surgical treatment when conservative management for fecal incontinence has failed.

Experiences and lessons

As demonstrated in our report, computed tomography findings may show mural rectal thickening with hypodense foci within the ano-rectal wall after injection of the ano-rectal bulking agent, which may mimic the appearance of an abscess or tumor; thus, it is important for clinicians to be cognizant of the endoscopic and radiological appearance of the ano-rectum after hyaluronic acid/dextranomer injection, to inquire about previous bulking agent injection in the anal canal, and to include this in the differential diagnosis.

Peer review

These authors showed the interesting finding of computed tomography and endoscopic findings after hyaluronic acid/dextranomer injection in the ano-rectal area. As it is demonstrated in their report, the computed tomography findings may show mural rectal thickening with hypodense foci within the ano-rectal wall, which may mimic abscess or tumor.

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CASE REPORT

Intraductal papillary mucinous neoplasm of the bile duct with gastric and duodenal fistulas

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Abstract

Intraductal papillary mucinous neoplasm (IPMN) of the bile duct is still rare and not yet understood despite of its increased incidence and similar clinicopathologic characteristics compared with IPMN of the pancreas. The fistula formation into other organs can occur in IPMN, especially the pancreatic type. To our knowledge, only two cases of IPMN of the bile duct with a choledochoduodenal fistula were reported and we have recently experienced a case of IPMN of the bile duct penetrating into two neighboring organs of the stomach and duodenum presenting with abdominal pain and jaundice. Endoscopy showed thick mucin extruding from two openings of the fistulas. Endoscopic suction of thick mucin using direct peroral cholangioscopy with ultra-slim endoscope through choledochoduodenal fistula was very difficult and ineffective because of very thick mucin and next endoscopic suction through the stent after prior insertion of biliary metal stent into choledochogastric fistula also failed. Pathologic specimen obtained from the proximal portion of the choledochogastric fistula near left intrahepatic bile duct through the metal stent showed a low grade adenoma. The patient declined the surgical treatment due to her old age and her abdominal pain with jaundice was improved after percutaneous transhepatic biliary drainage with the irrigation of N-acetylcysteine three times daily for 10 d.

Key words: Intraductal papillary mucinous neoplasm; Bile duct; Fistula; Acetylcysteine

Core tip: An intraductal papillary mucinous neoplasm of the bile duct with combined fistula formation into the stomach and the duodenum initially presented with jaundice and abdominal pain was introduced and after failed attempts of endoscopic suction of thick mucin through the two fistulas to resolve the jaundice, the patient's symptom was successfully resolved after the irrigations of N-acetylcysteine three times daily *via* after percutaneous transhepatic biliary drainage tube for 10 d.

Hong MY, Yu DW, Hong SG. Intraductal papillary mucinous neoplasm of the bile duct with gastric and duodenal fistulas. *World J Gastrointest Endosc* 2014; 6(7): 328-333 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i7/328.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i7.328

INTRODUCTION

Intraductal papillary mucinous neoplasm (IPMN) of the bile duct has been suggested to be the biliary counterpart of IPMN of the pancreas after wide acceptance of the nomenclature by the World Health Organization[1]. It represents a disease spectrum from benign to malignant and affected bile ducts exhibit marked dilatation because of mucin hypersecretion. Jaundice with cholangitis is sometimes complicated by the presence of intraductal tumor with tenacious mucoid impaction[2,3]. The fistula from penetration into other neighboring organs can be caused by high pressure due to mucin-filling of bile ducts and inflammatory stimulation[4]. IPMN of the bile duct with fistula formation into surrounding organs was relatively rare presentation compared with its pancreatic counter-

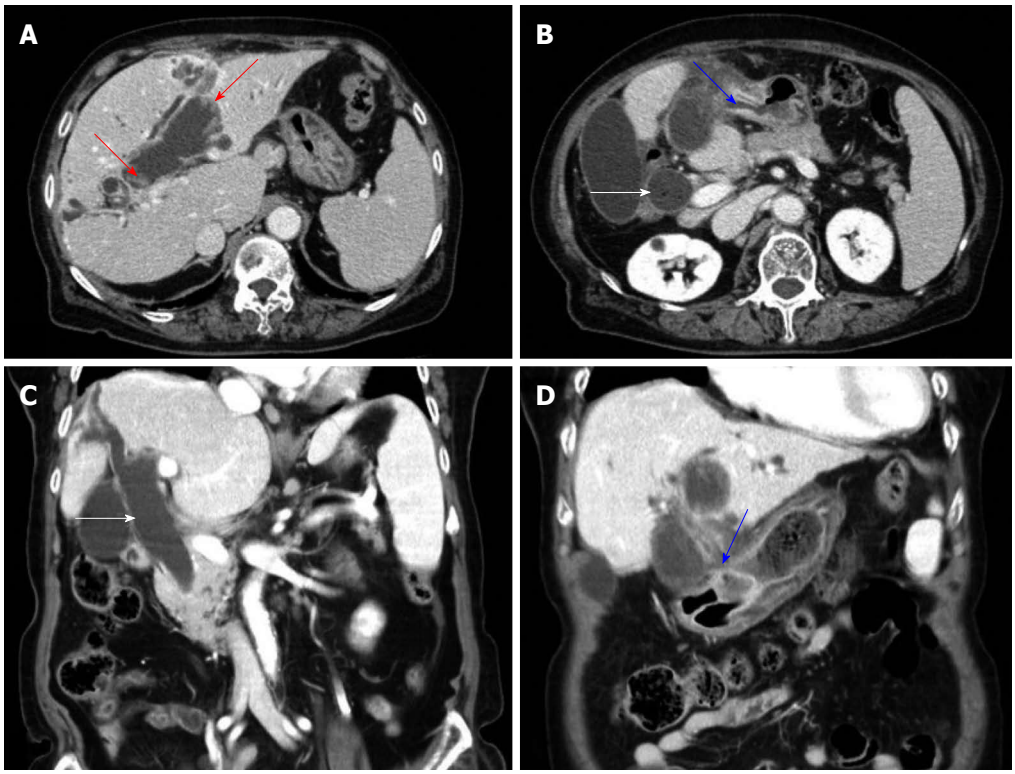

Figure 1 Computed tomography of the abdomen showed markedly dilated common bile duct (white arrows) and left intrahepatic duct with left intrahepatic duct penetrating into the antrum of stomach and fistula formation (blue arrows) and papillary projections along the dilated bile duct (red arrows) and no definite visible mass in the left intrahepatic duct (A-D).

part and to our best knowledge, only two cases of IPMN with the bile duct with one fistula into other organs were reported in the English literature[5,6] and here, we describe the first case of biliary IPMN with two fistulas into the stomach and duodenum.

CASE REPORT

An 87-year-old woman was admitted to our hospital because of acute right upper quadrant abdominal pain. On physical examination, palpable mass and tenderness of upper abdomen was noted. The complete blood count results showed white blood cell count of 3630/mm^3, hemoglobin of 7.8 g/dL, and platelet count of 188000/mm^3. The blood chemistry analysis showed total protein of 8.6 g/dL, albumin of 3.3 g/dL, total bilirubin of 2.7 mg/dL, aspartate aminotransferase of 29 U/L, alanine aminotransferase of 36 U/L, alkaline phosphatase of 249 IU/L, gamma-glutamyltransferase of 105 U/L, creatinine of 0.9 mg/dL, amylase of 45 U/L, and lipase of 35.6 U/L. Serum tumor markers of serum alpha-fetoprotein, CA19-9 and carcinoembryonic antigen were 1.9 ng/mL, < 2.0 U/mL and 7.5 ng/mL, respectively. Computed tomography (CT) of the abdomen showed markedly dilated common bile duct (CBD) and left intrahepatic duct (IHD) with left IHD penetrating into the antrum of stomach and fistula formation and no definite visible mass in left IHD (Figure 1). Endoscopy showed a round ulcerated lesion and extruding white thick mucin from the opening at the lesser curvature of the antrum during endoscopic suction and another wide opening of the fistula with mucin excretion proximal to the original papillary orifice (Figure 2). Cholangiogram obtained from the duodenal fistula near the papillary orifice showed moderately to severely dilated CBD and proximal left IHD with amorphous, partial intraluminal filling of the contrast in the bile duct (Figure 3). The lesion was strongly suspicious of IPMN of the bile duct with combined choledochogastric and choledochoduodenal fistulas. Four days after admission, serum bilirubin increased up to 5.0 mg/dL. Endoscopic suction to extract mucin to relieve jaundice caused by biliary mucinous obstruction and biopsy from the lesion of left IHD were planned using direct peroral cholangioscopy with ultra-slim endoscope (Olympus), but the removal of mucin by endoscopic suction with standard upper endoscope or ultra-slim endoscope was very difficult and failed because of very thick and high viscous mucin (Figure 4). And then, a partially covered metal stent was inserted through the choledochogastric fistula and endoscopic suction through the stent with ultra-slim endoscope also failed due to very thick mucin (blue arrow, Figure 5). Despite of approaching up to common hepatic duct level with ultra-slim endoscope through the choledochoduodenal fistula, target biopsy was not performed due to physical obstacle of large amount of very thick mucin, but instead, specimens were obtained from the proximal site of the fistula near left IHD through the metal stent in choledochogastric fistula and additional biopsy at the distal site of the choledochogastric fistula near the gastric antrum were done. Serum bilirubin level

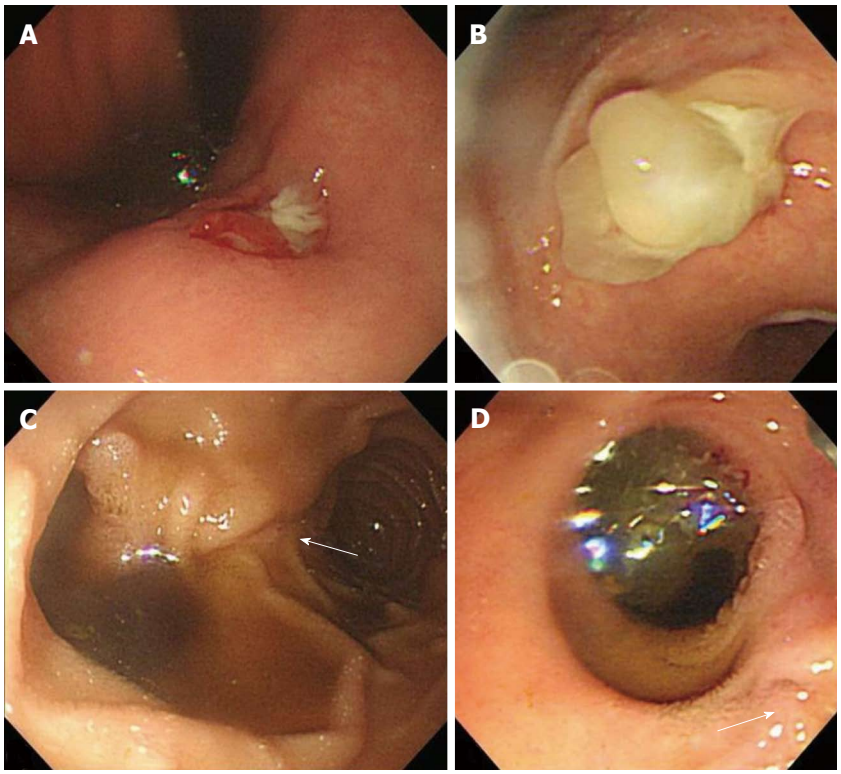

Figure 2 Endoscopic finding showed a round ulcerated lesion (A) and extruding white thick mucin from the opening at the lesser curvature of the antrum during endoscopic suction (B) and another wide opening of the fistula with mucin excretion proximal to the original papillary orifice (white arrows) (C, D).

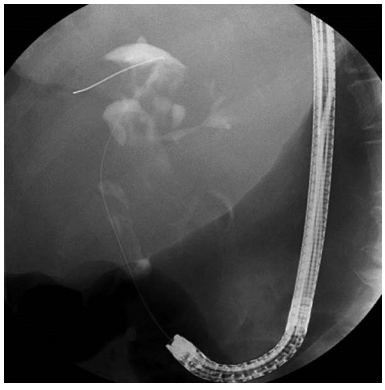

Figure 3 Endoscopic retrograde cholangiopancreatography finding through the choledochoduodenal fistula near the papillary orifice showed moderately to severely dilated common bile duct and proximal left intrahepatic duct with amorphous, partial intraluminal filling of the contrast.

was increased up to 6.0 mg/dL next day, but the patient refused surgical intervention and continued to complain abdominal pain and jaundice.

After insertion of percutaneous transhepatic biliary drainage (PTBD) catheter (Figure 5), the irrigations of N-acetylcysteine (300 mg) *via* the catheter three times a day for 10 d, abdominal pain resolved with decreased serum bilirubin level to 1.0 mg/dL and she was discharged with keeping the PTBD catheter and drainage bag. Pathology showed a low grade dysplasia from the proximal site of the choledochogatric fistula near the left IHD (Figure 6) and non-specific inflammation from the distal site of the fistula near the gastric antrum. She was still alive until recently during the follow-up period of 15 mo.

DISCUSSION

IPMN of the pancreas was first reported by Ohhashi *et al*[7] in 1982 and the clinical features are secretion of large amount of mucin by papillary neoplasm, dilatation of the main pancreatic duct or its branch ducts, slow growth with favorable prognosis, and chronic vague abdominal pain. The pathologic feature of the IPMN of the pancreas reveals the presence of a macroscopic intraluminal lesion and visible mucin on the surface of the tumor with solitary or diffuse intraductal growth[8]. IPMN of the bile duct is a variant of the bile duct malignancy and has a similar clinicopathologic features as its pancreatic counterpart because both the bile ducts and the pancreas develop from the ventral endoderm, although IPMN of the bile duct is associated with higher malignancy rate at the time of surgery than its pancreatic counterpart[9,10]. IPMN sometimes represents expansive progression with mucus extrusion and occasionally make a fistula penetrating into other organs. Fistula formation is divided into two types based on the mechanism, invasive penetration by malignant invasion and mechanical penetration by mucin extrusion with duct expansion[7].

In our case, the choledochogastric fistula formation was highly suggestive of mechanical penetration in that the specimen obtained from the distal part of the fistula near the stomach histologically showed non-specific inflammation, while the proximal part near the left IHD

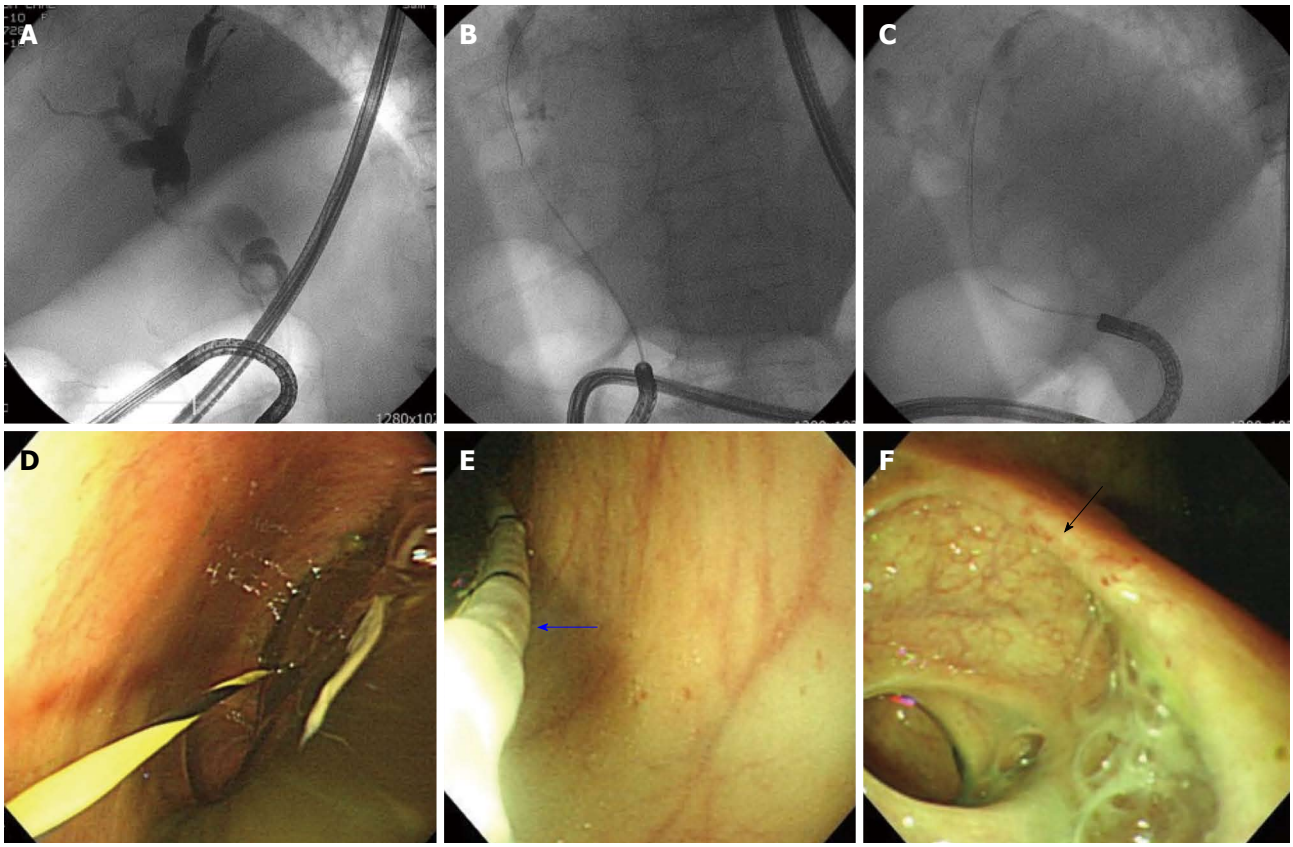

Figure 4 Cholangiogram using ultra-slim endoscope showed moderately to severely dilated common bile duct and both proximal intrahepatic duct with the amorphous, partial intraluminal filling in the bile duct (A-C) and the suction of thick mucus after advancement into bile duct and approach up to the cystic duct (black arrow) level using anchoring of the balloon catheter (blue arrow) was ineffective (D-F).

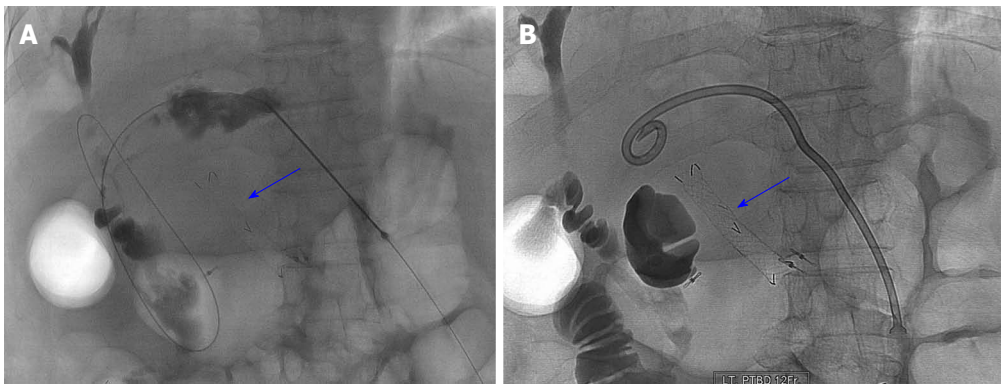

Figure 5 Cholangiogram obtained after contrast injection through the access needle into the left intrahepatic duct showed moderately to severely dilated left intrahepatic duct and common bile duct with the amorphous intraluminal filling consistent with the endoscopic retrograde cholangiopancreatography finding and the metal stent (blue arrow) previously inserted into the choledochogastric fistula for facilitating endoscopic suction of mucin through the stent was in place (A, B).

showed low grade adenoma.

The consensus guidelines for management of IPMN of the pancreas was well established since 2006, meanwhile, there has no published literature for making the accurate diagnosis and proper management of IPMN of the bile duct[11]. Although the majority of malignant IPMN of the bile duct demonstrates tumors or mural nodule in the bile ducts, in some cases the tumor is not visible in images or even in gross specimens and moderately to severely dilatation of the bile duct with mucobilia is the only finding like our case[2]. The diagnosis of IPMN of the bile duct was based on multimodality assessment of various imaging techniques. Ultrasonography is initial examination of biliary dilatation and stenosis with viscous mucin as fine echogenic findings. CT with magnetic resonance imaging have better delineation of biliary dilatation with tumor location, extent and volume (stage). ERCP is a relatively invasive examination

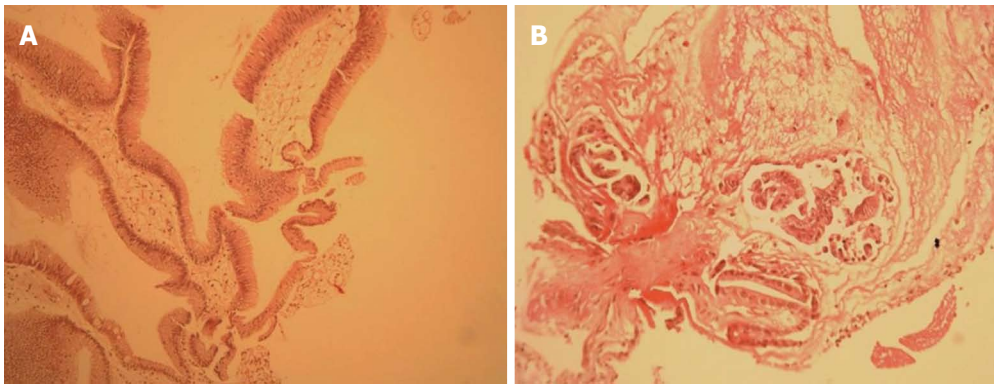

Figure 6 Pathology of the specimen from the proximal portion of the choledochogastric fistula showed a low grade adenoma [hematoxylin and eosin stain, × 200 (left), × 400 (right)].

and shows mucobilia as a filling defect of contrast in bile duct and endoscopic ultrasound (EUS) can be used for detecting mural nodule or solid mass with local invasion and cytological analysis obtained by fine needle aspiration[1,3,11]. EUS examination was not performed in our patient because of no visible mass in the CT and ERCP findings.

The insertion of multiple uncovered metal stents has been shown to be feasible in the patients of IPMN of the pancreas with biliary obstruction by mucoid impaction[12], but the insertion of multiple metal stents alongside each other to facilitate biliary drainage could not apply to the patient of severely dilated bile duct with thick mucoid impaction and no specific stenosis like our case.

The mucolysis of antioxidant N-acetylcysteine (NAC) was widely used in the management of the symptom of the chronic obstructive pulmonary disease and other respiratory conditions such as idiopathic pulmonary fibrosis[13,14] and the usefulness of the dissolution of the renal stone by the irrigation with NAC *via* percutaneous nephrostomy was reported[15]. A case of the effectiveness of infusion of NAC through nasobiliary catheter for advanced biliary IPMN was recently reported[16]. In our case, the bilirubin level and her abdominal pain was improved by the intermittent infusions of NAC (300 mg) three times a day for 10 d through the PTBD catheter. Choledoscopy *via* PTBD after resolution of abdominal pain and jaundice with multiple irrigations of NAC was intended for further detailed examination of IHD, but she denied and only request symptom relief.

In summary, IPMN of bile duct with combined two fistulas into the stomach and the duodenum presented with abdominal pain and ongoing jaundice due to thick mucoid impaction in the bile duct was successfully treated with the irrigation with NAC for 10 d.

COMMENTS

Case characteristics

The patient presented with abdominal pain and jaundice.

Clinical diagnosis

Intraductal papillary mucinous neoplasm (IPMN) of the bile duct with combined fistulas of the stomach and the duodenum.

Differential diagnosis

Mucin-producing cholangiocarcinoma or biliary papilloma(tosis) or papillary cholangiocarcinoma were considered because of mucin hypersecretion and moderately to severely dilation of the bile duct on imaging studies.

Laboratory diagnosis

Acute cholangitis accompanied with IPMN of the bile duct was based on fact that initial serum total bilirubin level was 2.7 mg/dL and reached up to 6 mg/dL six days after admission.

Imaging diagnosis

IPMN of the bile duct with combined fistulas of the stomach and the duodenum was based on multimodality imaging and endoscopic finding.

Pathological diagnosis

Histologic finding of the specimen obtained from left intrahepatic bile duct through the inserted metal stent in choledochogastric fistula showed IMPN of the bile duct with low grade dysplasia.

Treatment

The patient's abdominal pain with jaundice was settled after the multiple irrigations of N-acetylcysteine (NAC) through percutaneous transhepatic biliary drainage (PTBD) catheter for 10 d.

Related reports

Two case reports of IPMN of the bile duct accompanied with choledochoduodenal fistula published in English were shown in references 5, 6.

Experiences and lessons

Clinicians should consider that multiple irrigations of NAC *via* PTBD tube is an alternative therapeutic option for IPMN of the bile duct with thick mucoid impaction accompained with cholangitis after failed endoscopic suction of mucin.

Peer review

The authors presented a rare, interesting case of IPMB with combined fistula formation into the stomach and the duodenum. This case is very interesting.

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REVIEW

New aspects of modern endoscopy

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Abstract

The prognosis for patients with malignancies of the gastrointestinal-tract is strictly dependent on early detection of premalignant and malignant lesions. However, small, flat or depressed neoplastic lesions remain difficult to detect with these technologies thereby limiting their value for polyp and cancer screening. At the same time computer and chip technologies have undergone major technological changes which have greatly improved endoscopic diagnostic investigation. New imaging modalities and techniques are very notable aspects of modern endoscopy. Chromoendoscopy or filter-aided colonoscopy (virtual chromoendoscopy) with high definition endoscopes is able to enhance the detection and characterization of lesions. Finally, confocal laser endomicroscopy provides histological confirmation of the presence of neoplastic changes. The developing techniques around colonoscopy such as the retro-viewing colonoscope, the balloon-colonoscope or the 330-degrees-viewing colonoscope try to enhance the efficacy by reducing the adenoma miss rate in right-sided, non-polypoid lesions. Colon capsule endoscopy is limited to identifying cancer and not necessarily small adenomas. Preliminary attempts have been made to introduce this technique in clinical routine.

Key words: Modern endoscopy; High definition endoscopy; Virtual chromoendoscopy; Autofluorescence; Endomicroscopy; Molecular imaging

Core tip: Today a competition has started between the existing endoscopic methods to be the most efficient in detecting the premalignant condition in the gastrointestinal tract. This review illustrates the current status of the available techniques in endoscopy with a focus on screening colonoscopy.

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INTRODUCTION

Rapid advancements in computer and chip technology and the resulting technical options in imaging and image processing have influenced modern endoscopy today as never before in the past. A large number of technical innovations have been introduced in diagnostic endoscopy in the last few years, with the aim of improving the detection and characterization of pathological changes in the gastrointestinal tract. High-resolution image display in endoscopes of the newest generation is supported by virtual chromoendoscopy, a type of staining of mucous membranes at the press of a button. Classical chromoendoscopy is also significant for specific indications. Recent microscopic procedures such as endomicroscopy and endocytoscopy are able to not only predict pathological changes on the basis of their surface or vascular pattern, but also directly visualize the cellular architecture of the mucosa. The better the quality and clarity of images, the better the patient can be cared for. Thus, the main purpose of endoscopy can be achieved, which is early and timely detection of malignant changes. Modern endoscopy systems provide major technical innovations for

each of the three important consecutive diagnostic steps. All of these innovations can be utilized for optimized diagnostic investigation: (1) Detection-identification of changes (circumscribed *vs* diffuse); (2) Characterization of circumscribed lesions (prediction about the benign or malignant nature of the lesion); and (3) Confirmation by means of cell analysis (conventional or *in vivo* histology).

HIGH DEFINITION ENDOSCOPY

High definition became a catchword after the introduction of high definition television (HDTV) in television and entertainment technology. It produced high-resolution images that were practically incomparable with, and unobtainable by, the previously used transmission technology (PAL) in endoscopy. Further development of chip technology (CCD chip), by which more than one million pixels per image can be analyzed today, led to the achievement of much greater resolution in so-called high-resolution endoscopy than in video endoscopy of the first generation[1]. The most recent color chips, although miniaturized, currently permit greater pixel density and a resolution of more than one million pixels per video image, which can now be visualized by the new television standard of HDTV with as many as 1080 video lines per image[1]. This has greatly enhanced image quality compared to standard resolution (SR) with 576 lines. Thus, currently available high-resolution endoscopy systems (high definition or HD) achieve a resolution of 1400 x 1080 pixels. Combined with conventional or virtual chromoendoscopy, preliminary clinical data indicate that the technical advancement of HD endoscopy is a decisive element of better diagnostic investigation of early forms of cancer, and is thus able to exert an immediate impact on the prognosis of the disease for patients[2]. In a large retrospective study Buchner was able to show, in 2430 patients, a significant rise in the detection rate of adenomas (HD 28.8% *vs* SR 24.3%, $P = 0.012$) by HD endoscopy.

These data were confirmed in a prospective study from Mainz, in which a significant rise in the detection rate of adenomas - especially flat adenomas - was noted in 200 patients who underwent preventive examination[3,4]. In a recently published meta-analysis, the authors report a diagnostic gain of 3.8% by the use of the HD technique, but also mention the heterogeneity of previously obtained study data[5-9] (Table 1).

CHROMOENDOSCOPY

The color dyes or pigments used in chromoendoscopy either react with intracellular structures of mucosa (*absorption*) or remain on the mucosal surface (*contrast stain*) (Table 2). The most commonly used staining materials in the upper gastrointestinal tract are Lugol's solution (changes in squamous epithelium) and acetic acid (changes in the columnar epithelium). In the lower gastrointestinal tract one usually employs indigo carmine or methylene blue[10,11]. The somewhat greater expenditure of time and the large number of available staining materials, as well as uncertainty about the quantity and concentration of staining materials have prevented chromoendoscopy from being established in the Western world. However, our knowledge of the morphology of early cancers in the upper and lower gastrointestinal tract has been enhanced very markedly by the use of chromoendoscopy, and has sensitized clinicians to the necessity of early detection, particularly that of flat lesions[12-17]. A number of prospective studies, especially those from Asia, have clearly demonstrated the superiority of chromoendoscopy compared to pure white light endoscopy[12-17]. A recent American multicenter study confirmed that the prevalence of flat neoplasias in screening colonoscopies by chromoendoscopy is 10% - which is three-fold higher than the rates reported thus far[18]. Conclusion: Targeted spraying of color in the presence of mucosal and vascular changes of irregular flatness is recommended in order to unmask flat adenomas and early carcinomas. Chromoendoscopy facilitates the detection of colorectal neoplasias, and can also be used to characterize the identified lesions. Kudo's pit pattern classification standardizes surface analysis. In a meta-analysis of 22 studies, a sensitivity of 94% and a specificity of 82% was established for the differentiation of neoplastic and non-neoplastic lesions for the pit pattern classification[13]. Chromoendoscopy is especially valuable for monitoring patients with ulcerative colitis. Here one should not use targeted staining but pan-chromoendoscopy. This type of chromoendoscopy permits detection of more numerous colitis-associated neoplasias as well as identify more patients with neoplasias[19-25]. A recent meta-analysis mentions 14.3 as the "number needed to treat". In other words, by performing 14 colonoscopies with pan-chromoendoscopy one is able to diagnose one additional patient with intraepithelial neoplasias. Chromoendoscopy is currently experiencing a renaissance because the combination of high-resolution endoscopy and intravital staining provides an especially detailed view of the surface structure of mucosa.

VIRTUAL CHROMOENDOSCOPY

Owing to the previously described modern processor technology of high-resolution endoscopy systems and the possibility to add color by pressing a button and activating a color filter, virtual coloring is currently receiving special attention in endoscopy. The procedure of so-called virtual chromoendoscopy modulates, by the press of a button and with no loss of time, the spectrum of visible light so that the mucous membranes can be visualized in various "missing colors"[1]. The effect of such color accents is that individual components of the mucosa, such as the surface pattern or vascular structures of the mucous membranes can be depicted more clearly[2]. The different color spectrums are produced either by modulating the incoming light with filters (NBI technique), or by software-based processing (so-called post-processing) of the reflected light (FICE, *i*-scan technique

Table 1 High definition *vs* standard colonoscopy for the detection of colorectal adenomas

Ref.	Study design, study objective	Wide angle	No. of pts.	Adenoma detection rete	*P* value	Absolute increase	Relative increase
East *et al*[30]	Cohort	No	130	65	0.20	11%	18%
Pellisé *et al*[77]	Randomized	Yes	620	26	0.85	1%	4%
Burke *et al*[78]	Cohort	Yes	852	23	0.36		13%
Tribonias *et al*[79]	Randomized	Yes	390	54	0.16	8%	16%
Buchner *et al*[3]	Cohort	Yes	2430	27	0.01	4.2%	17%
Hoffman *et al*[4]	Randomized	No	220	38	0.001	25%	192%

Table 2 Vital stains in endoscopy

Stain	What is stained	Current use
Vital stains		
Methylene blue	Small/large intestinal cells	Chronic ulcerative colitis
		Gastric intestinal metaplasia and early cancer gastric cancer
		Colon polyps/neoplasms
Lugol's iodine	Normal glycogen containing squamous cells	Oesophageal squamous cell cancer and dysplasia
Cresyl violet	Small and large intestine crypts	Colonic polyps/neoplasms
	Oesophagus and gastric mucosa	Barrett`s esophagus
		Early gastric cancers
Contrast stains		
Indigo carmine	Cells are not stained, appearances caused by contrast pooling	Chronic ulcerative colitis
		Gastric intestinal metaplasia and early cancer gastric cancer
		Colon polyps/neoplasms
Acetic acid	Reversible interaction between the acetic acid and the cell structures	Barrett´s esopahus

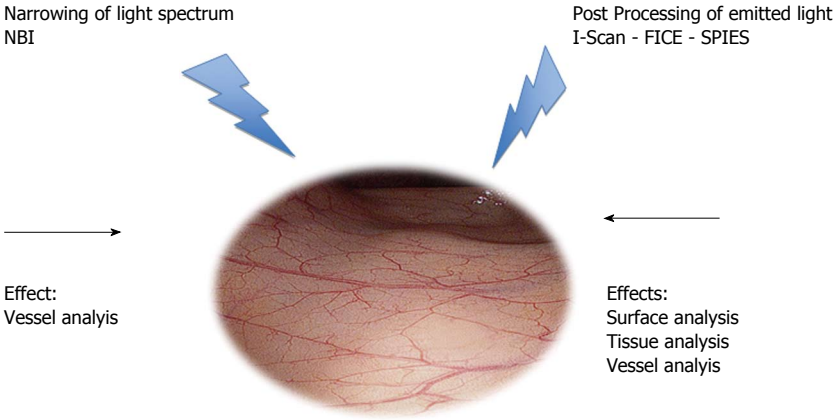

Figure 1 Digital chromoendoscopy. Digital chromoendoscopy can be achieved by simply pressing a button on the endoscope. NBI focuses on vessel architecture by narrowing the light spectrum which is emitted to the mucosa. Fujinon Intelligent Color Enhancement System, *i*-scan and STORZ Professional Image Enhancement System are technologies, which use the reflected light for post-processing light filtering which is used to obtain different effects (like surface, tissue and vessel enhancement). (mod. advanced imaging in endoscopy 2009).

or SPIES)[1,2] (Figure 1). Thus, modern filter technology is replacing, to an increasing extent, the more time-consuming procedure of chromoendoscopy. An increasing body of data indicates that the efficacy of virtual chromoendoscopy is equivalent to that of intravital staining (with the exception of ulcerative colitis) in the upper and the lower gastrointestinal tract.

NBI

NBI (Olympus, Japan) is the oldest established method of virtual chromoendoscopy. While conventional white light video endoscopy utilizes the entire visible spectrum of light (400 to 700 nm) to produce an image from the complementary colors red, green and blue, narrow-band imaging (NBI, Olympus, Japan) is based on an integrated filter system that narrows the spectrum of complementary colors and thus accentuates the blue light spectrum. In contrast to red light, the light waves of the blue and green spectrum do not penetrate the deeper layers of tissue. Instead, they are absorbed by blood vessels at the level of the mucous membranes and thus provide clear contrast enhancement of the architecture of mucosal vessels[26]. Contrary to expectations, however, the first large multicenter studies showed no significant improvement in detection rates of colorectal neoplasias on com-

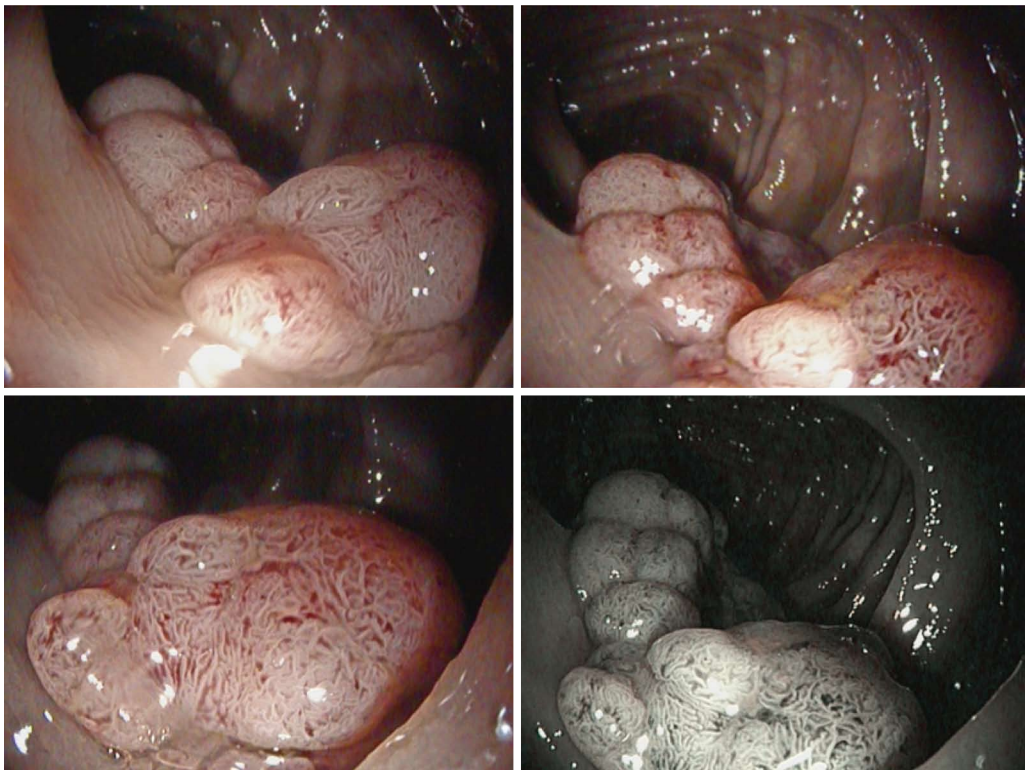

Figure 2 Virtual chromoendoscop using STORZ Professional Image Enhancement System of colorectal lesions.

parison of high-resolution colonoscopy with and without NBI[27-29].

East *et al*[30] attributed the low detection rates to the poor illumination of the endoscopic image under NBI compared to conventional endoscopy. In a further recent prospective investigation, the authors attribute their high detection rate of adenomas (WL 58.3% and NBI 57.3%) to the excellent resolution of high-definition endoscopy and not to NBI but showed, in contrast to other studies, NBI to be superior in the detection of flat adenomas (21.4% *vs* 9.3%, $P = 0.019$)[31]. Analogous to chromoendoscopy, after expiry of the corresponding learning curve NBI may be utilized with great benefit for prediction of the malignant or benign nature of lesions by way of neoplastic and non-neoplastic lesions. In the upper gastrointestinal tract, the combination of high-resolution endoscopy and NBI imaging permits better diagnostic investigation of Barrett's esophagus. According to a new classification provided by Singh *et al*[32], mucosal forms may be graded into four types on the basis of their vascular and epithelial structures. Thus, epithelium of the cardia, Barrett's epithelium, and Barrett-associated neoplasia can be distinguished from each other with a high degree of predictive accuracy (positive predictive value: 100%, 88% and 81%). Similar data were reported in several studies performed by Jacques Bergmann's group in Amsterdam[33-36]. However, analogous to the colon, a decisive improvement in the diagnostic investigation of neoplasias in Barrett's esophagus appears to be achieved mainly by high-resolution endoscopy[37].

ISCAN, FICE AND SPIES

The filters *i*-scan (Pentax, Europe), SPIES (Karl Storz, Europe) and FICE (Fujinon, Europe) are based on processor-integrated software applications that alter the wavelength ranges of reflected light and thus, in contrast to NBI technology, offer a number of filter options[2]. In addition to depicting vessels, portions of tissue and surface structures can be visualized in a selective and accentuated manner. *I*-scan technology is based on an integrated software tool that enhances the surface with the aid of the function of "surface enhancement" and, by additionally switching on specific color filters, permits virtual chromoendoscopy to be performed. Initial published studies have confirmed the efficacy of this procedure. Thus, reflux lesions in the upper gastrointestinal tract (UGI) could be diagnosed more accurately by the use of surface enhancement[38]. In the lower gastrointestinal tract (LGI) it was found that the *i*-scan function is equivalent to chromoendoscopy for the diagnosis of neoplastic lesions in respect of detection rates and characterization. A recently published study showed a significant enhancement of detection rates, particularly those of flat adenomas, by the use of surface enhancement (SE mode) in combination with high-resolution endoscopy[4,39]. FICE (Fujinon Intelligent Color Enhancement System) and SPIES (STORZ Professional Image Enhancement System) are other types of computer-assisted virtual chromoendoscopy (Figure 2). In both prospective studies on FICE, the authors Chung and Pohl achieved excel-

lent characterization of lesions with the aid of FICE, although a significant advantage in terms of detection rates of adenomas was not registered in either study[40,41].

Colon capsule endoscopy

A variety of media campaigns and other initiatives have surprisingly led to only a small impact to promote screening colonoscopy[42]. The reasons for the limited take-up of CRC screening, especially of colonoscopy, are diverse. Apart from general doubts and fears, factors such as perception of colonoscopy as painful and unpleasant may have contributed to the lack of uptake.

Capsule endoscopy was introduced some years ago primarily for small bowel diagnostics, but has been extended to the colon with a modified capsule used for capsule colonoscopy[43,44]. PillCam colon-capsule provides a screening solution, which is minimally invasive, safe, does not require sedation. It is well accepted by patients, although still requiring thorough bowel cleaning and is mainly recommended to people who have so far denied CRC screening programs[44].

It is an easy to perform examination with an excellent negative predictive value for application in screening purposes under routine conditions. However, diagnostic accuracy for relevant size polyps (*i.e.*, sensitivity) is low. First studies have has been shown to be about 65%-75% accurate for adenoma detection in the large bowel when compared with colonoscopy[45-49]. But with capsule colonoscopy there is a fourfold increase in endoscopic screening, with men in particular finding capsule colonoscopy more acceptable. Colon capsule screening is expensive, because there are no screening programs supporting colon capsule as the primary choice. Thus, the colon capsule has to be paid by the patient, which also hindered broad acceptance.

AUTOFLUORESCENCE AND SPECTROSCOPY

Autofluorescence endoscopy is another advancement in endoscopy, which is playing an increasingly significant role in the early detection of dysplasias. The principle of fluorescence diagnosis is based on the fact that light of a specific wavelength (approximately 400-500 nm) is not merely absorbed and reflected in tissue, but also causes fluorescence produced by auto fluorophores or exogenously introduces fluorophores [*e.g.*, 5-aminolevulinic acid (5-ALA)][50,51]. A variety of pathological processes such as inflammation, ischemia, and adysplasia demonstrate different fluorescence behavior compared to normal tissue. Therefore, this technology is also known as red flag technology. However, a disadvantage of the method is the fact that autofluorescence is not specific for neoplasia and is therefore associated with a high rate of false positive diagnoses. To enhance the specificity of this method, it is usually combined with HD endoscopy and NBI for characterization of the detected lesions; this is known as endoscopic trimodal imaging[52-54]. In initial studies on the upper and lower gastrointestinal tract, autofluorescence was tested successfully in patients with Barrett's esophagus and ulcerative colitis[55]. We will have to wait and see whether the results of further studies will help to establish this promising method.

Field carcinogenesis is another highly interesting development. We know that certain factors even predispose mucous membranes outside the actual neoplasia for the development of neoplasia. This fact is utilized in field carcinogenesis. By measuring suitably filtered elastic light dispersion, gradients in blood supply and oxygen depletion, culminating in lesions, could be measured in the colon. In the future rapid probe investigation in the rectum might enable the investigator to predict lesions at a greater distance[56].

Endomicroscopy

Endomicroscopy is the first endoscopic procedure that, in addition to the analysis of surface structure, permits microscopic analysis of cellular structures of the mucous membranes *in vivo*[57,58]. The major difference compared to all other techniques is that the benign or malignant nature of a lesion cannot be predicted, but can be determined immediately *in vivo* by microscopic investigation. Confocal laser endoscopy (endomicroscopy) is based on argon laser with a wavelength of 488 nm (blue laser light), so that as many as 1012 × 1012 pixels per endomicroscopic image can be analyzed and evaluated after application of a fluorescent dye (usually fluorescein) by the use of a miniaturized scanner in the endoscope, or by the use of a forward deployed probe. While the first publications established the application and feasibility of this approach in patients, a number of studies have been performed since 2004 on the upper and lower gastrointestinal tract. All of these show that- assisted by simple classification systems-the endoscopist is able to perform microscopic tissue diagnosis on site[57-60] (Figure 3). Thus, confocal endomicroscopy is currently a well established method and is frequently used in conjunction with chromoendoscopy to first detect suspicious lesions and then analyze them exactly by endomicroscopy. This does not by any means replace pathological investigation. Rather, it permits very reliable prediction of relevant findings by endomicroscopy during the investigation itself so that classical biopsies of the mucous membranes can be minimized and only targeted biopsy specimens (so-called smart biopsies) can be taken[22]. In a large randomized study in patients with ulcerative colitis of long duration we were able to show that the number of biopsies could be reduced by a factor of ten while the diagnosis of colitis-associated dysplasias was increased fourfold. Investigations on Barrett's esophagus confirmed the role of endomicroscopy in immediate resection after *in vivo* diagnosis of a neoplasia; the evaluation of resection margins was also tested successfully[61,62]. Furthermore, endomicroscopy offers the option of visualizing physiological as well as pathophysiological processes in human beings during endoscopy. The most striking example of this approach is the identification of cellular desquama-

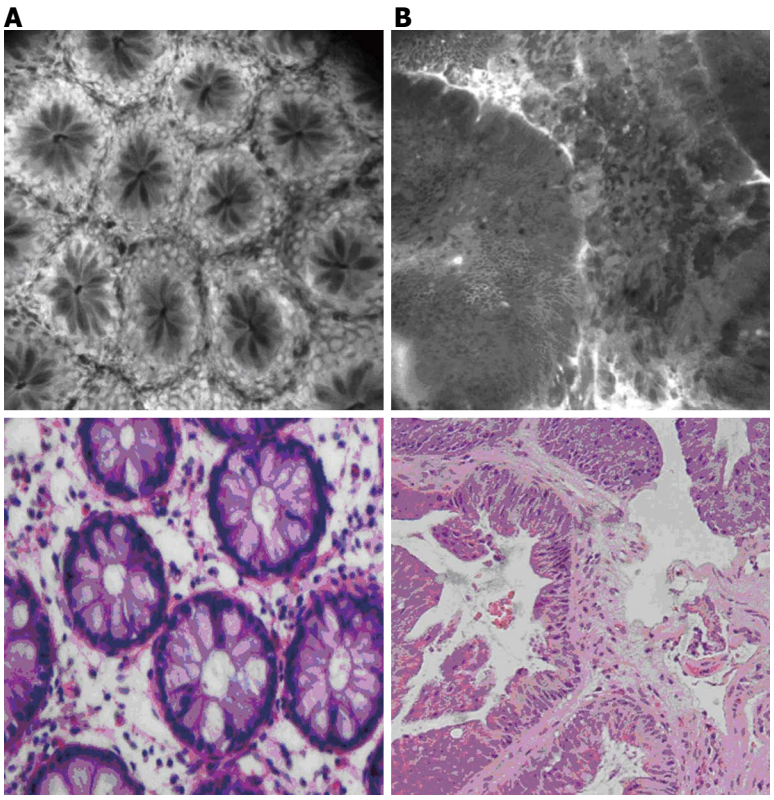

Figure 3 Confocal Endomicroscopy in normal colonic epithelium (A) and of a colonic dyspalsia (B).

tion in the bowel, which is initially a manifestation of physiological regeneration. However, in patients with Crohn's disease and ulcerative colitis there was an increase in cell desquamation with the effect of subsequent closure of the gaps thus created[63]. The development of endomicroscopy is a prerequisite for molecular imaging because, as an *in vivo* procedure it offers the option of low-artifact observation of cellular processes in metabolism, which could markedly enhance our understanding of pathophysiology[64,65]. Thus, even the interaction of antibodies or peptides with the corresponding receptors can be observed live, which may be of fundamental significance in planning treatment with biologic agents[66,67]. It is still not possible to use molecular imaging in clinical routine, but preliminary human studies as well as animal experiments have demonstrated the new optic possibilities it offers in endoscopy.

MOLECULAR IMAGING

Molecular imaging is one of the major bears of hope in the field of cancer research and early detection because it renders pathological changes visible at the cellular level[66]. The optic form of molecular imaging, which provides colored views of suspicious areas on the endoscopy image, can already be used *in vivo* for various types of tumors[66-70]. By the use of molecular probes usually applied exogenously, one can visualize specific surface molecules or metabolic processes that occur selectively in the target tissue. Thus, colorectal carcinomas could be stained in targeted fashion at the molecular level by marking antibodies to epitopes like the epidermal growth factor receptor (EGFR) or the vascular endothelial growth factor (VEGF); this was achieved in mouse models as well as in human tissue[66,69,70]. The advantage of antibodies is their highly specific binding to their target structure, which causes marked contrast between (stained) diseased and (non-stained) healthy tissue. Besides, in disease the biological function of the target structure is usually well established and partly even a component of current therapy protocols, such those for cetuximab or panitumumab (against EGFR) or bevacizumab (against VEGF). Molecular imaging requires special endoscopes that either permit the detection of lesions on the overview image or microscopic characterization of molecular processes during endoscopy. As a result, the use of molecular imaging for endoscopy has not been established in large patient populations, but is very likely to fundamentally influence future clinical algorithms and has already brought about a significant advancement in clinical and basic research by enhancing our comprehension of gastrointestinal diseases.

TECHNOLOGIES ON THE HORIZON

An apparently leading cause of missed polyps during colonoscopy is attributed to polyps that are located behind haustral folds in the colon, and are therefore hidden from the conventional, forward-viewing endoscope optics. It was demonstrated that occasional straightening of haustral folds during colonoscopy, by a plastic cap mounted on the endoscope tip, increases the polyp detection yield[71]. A 6185 patient study by Westwood reported a miss-rate of 12.2% in the cap-assisted colonoscopy

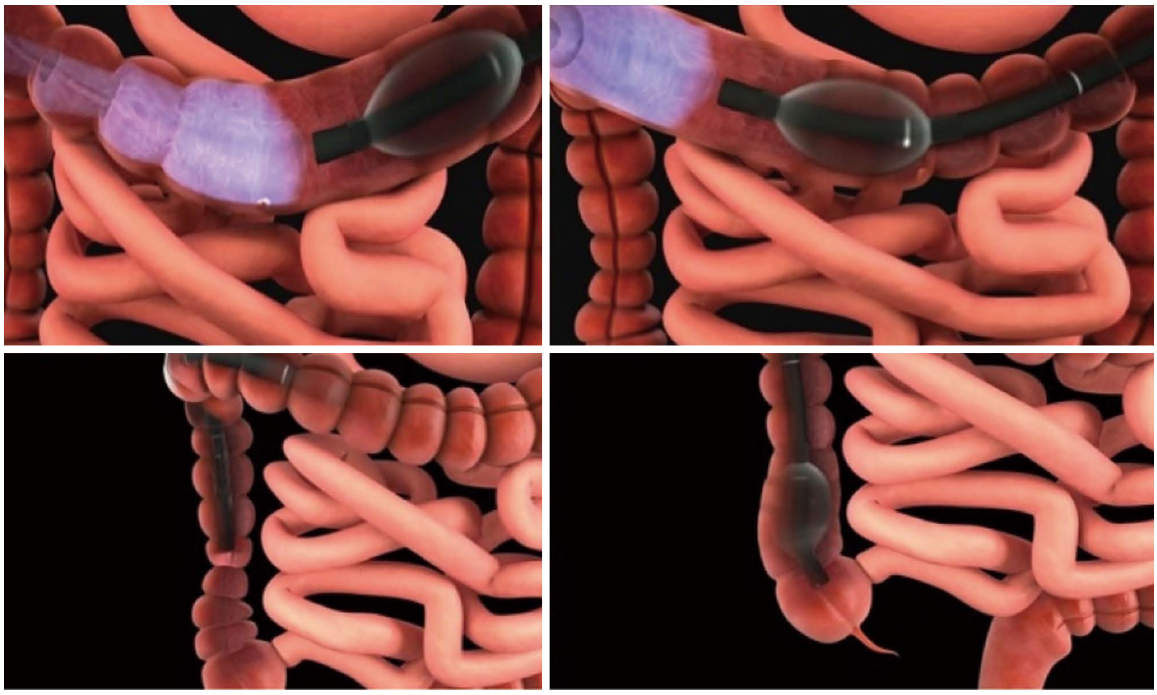

Figure 4 GEye balloon colonoscopy with inflated balloon at the distal tip of the colonscope the balloon is inflated to straight intestinal folds in the colon.

group *vs* 28.6% miss rate in the standard colonoscopy group, implying a positive effect of cap employment on polyp detection rate[71]. In contrast, another study performed by Tee in 400 subjects, reported that there was no significant polyp detection rate difference detection standard colonoscopy and cap-assisted colonoscopy (31.3% *vs* 32.8%, respectively)[72]. Recently, a retro-viewing device (Third Eye Retroscope, Avantis Medical, Sunnyvale, CA) was introduced for use during colonoscopy with standard endoscopes and was analyzed in a single randomized controlled trial (same-day tandem examinations)[73]. This technique is aimed to allow inspection of the proximal surface of haustral folds, which is not in the line-of-sight of the endoscope's forward-viewing optics, thereby allowing detection of polyps that are located behind such folds. Intention-to-treat and per-protocol analyses included 395 and 349 patients, respectively. Using the retrograde-viewing device was associated with an increase in the total number of adenomas detected of 23% compared with standard colonoscopy (after correcting for the second-pass effect) and the relative risk of missing lesions with standard colonoscopy compared with colonoscopy using the retrograde-viewing device was 2.56 for polyps ($P < 0.001$) and 1.92 for adenomas ($P = 0.029$). Previous uncontrolled studies also suggested that the retrograde-viewing device may allow detecting 10% more adenomas compared to standard colonoscopy[74]. But in the intention to treat analysis, the benefit in the total number of adenomas detected dropped from 23% to 14% and the relative risk of missing lesions with SC compared with colonoscopy using the retrograde-viewing device became not significant for adenomas. Furthermore the cost of this technique is still relatively high and needs the approval of more prospective studies.

The new G-Eye system is a balloon-colonoscope (NaviAidTM G-EYE, Smart Medical Systems, Israel), comprising a standard colonoscope having a re-processable, permanently integrated balloon at its distal tip. The balloon pressure is controlled through a unique inflation system providing pre-determined, user-selectable, anchoring and intermediate (low) pressure levels (Figure 4). First results from a prospective multicenter back to back study included 126 patients. The G-Eye balloon-colonoscopy detected 23 additional polyps, that means a promising 115% additional adenoma detection rate. Balloon-colonoscope's additional detection rate ratio, calculated as the ratio between balloon-colonoscopy 2nd pass additional detection and balloon colonoscopy 1st pass miss-rate, is 25.5 (115/4.51)[75]. The results from this first multicenter study are very promising and further confirming studies are ongoing. Another reason for a high adenoma miss rate is discussed due to inadequate visualization of the proximal aspect of colonic folds and flexures. Full spectrum endoscopy (FUSE, EndoChoice, Alpharetta, GA, United States) utilizes unique imaging technology, which allows the endoscopist to view 330 degrees while maintaining identical standard colonoscope technical features (Figure 5). The results for this new technique were a 32.9% incremental polyp detection rate (per patient analysis) and a 39/49 (79.6%) incremental polyp detection rate (per polyp analysis) using this new FUSE colonoscope. Furthermore on subsequent FUSE colonoscopy, there were an additional 15/88 (17.1%) subjects who had at least one adenoma detected, yielding an additional 21 adenomas. This is a incremental 17.1% adenoma detection rate (per patient analysis) and a 21/28 (75.0%) incremental adenoma detection rate (per adenoma analysis) using FUSE colonoscopy[76]. But as with all new technology they are

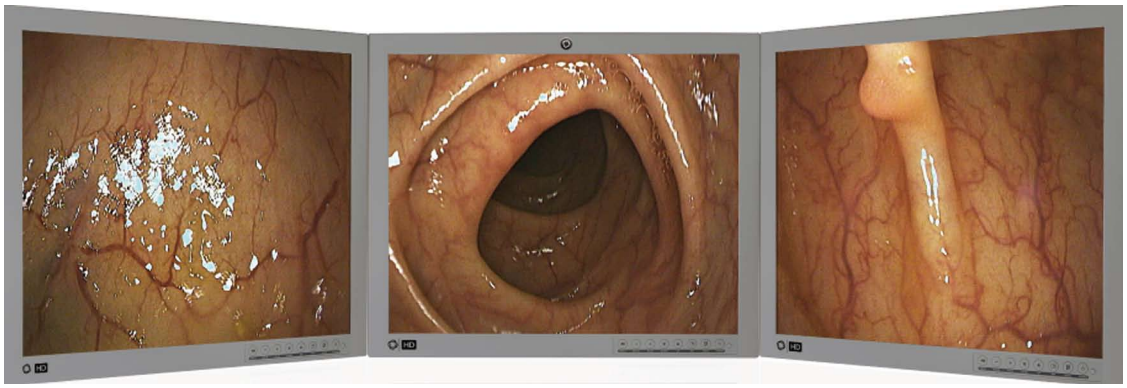

Figure 5 Full spectrum endoscopy colonoscopy utilizes unique imaging technology, which allows the endoscopist to view 330 degrees while maintaining identical standard colonoscope technical features. Property of full spectrum endoscopy, EndoChoice, Alpharetta, GA, United States.

often accompanied by initial enthusiasm, but have to be proved in a more clinical setting and practice.

CONCLUSION

New techniques of diagnostic endoscopy are being developed with rapid speed. To achieve early identification of precancerous lesions and then initiate targeted and definitive endoscopic therapy immediately, the modern endoscopist must keep abreast with new technologies. In addition to more frequent detection of neoplasias, the latter should also be characterized in greater detail on site in order to better estimate the extent of any required endoscopic intervention. In this endeavor the endoscopist is supported by common filter technologies. So-called virtual chromoendoscopy is in the process of replacing classical chromoendoscopy because it is equally effective but requires less time. Endomicroscopy signifies a crucial advancement of gastrointestinal endoscopy in the last few decades. Endomicroscopy permits, for the first time, *in vivo* investigation of mucous membranes at the cellular level. In addition to the fact that simultaneous histological investigation can be performed along with endoscopy, some diseases can now be diagnosed reliably for the first time, and physiological as well as pathophysiological processes can be observed. This development has caused molecular imaging to gain center stage in endoscopy. Apart from the fact that it has simplified better detection of suspicious lesions, oncological therapy approaches can be planned and understood better. Although gastrointestinal endoscopy has become much more complex now, the optic details provided by the new technologies will contribute significantly to improving the efficiency of the diagnosis and treatment of gastrointestinal endoscopy.

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MINIREVIEWS

Endoscopic retrograde cholangiopancreatography in patients with altered anatomy: How to deal with the challenges?

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) in patients with surgically altered anatomy is challenging. Several operative interventions of both the gastrointestinal tract and the biliary and/or pancreatic system lead to altered anatomy, rendering ERCP more difficult or even impossible with a conventional side-viewing duodenoscope. Adapted endoscopes are available to reach the biliopancreatic system and to perform ERCP in patients with altered anatomy. However, both technical difficulties and complications determine the procedure's success. Different technical approaches have been described and are highly dependent on local expertise and endoscopic equipment. Standardized practical guidelines are currently unavailable. This review focuses on the challenges encountered during ERCP in patients with altered anatomy and how to deal with them. The first challenge is reaching the papilla or the bilioenteric/pancreatoenteric anastomosis in the patient with postoperative altered anatomy. The second challenge is the cannulation of the biliopancreatic system and performing all conventional ERCP interventions and the third challenge is the control of possible complications. The available literature data on this topic is reviewed and illustrated with clinical cases.

Key words: Endoscopic retrograde cholangiopancreatography; Altered anatomy; Billroth; Roux-en-Y

Core tip: Endoscopic retrograde cholangiopancreatography in patients with surgically altered anatomy is difficult and faces several challenges. There are three important challenging steps in this endoscopic procedure: reaching the papilla or the bilioenteric/pancreatoenteric anastomosis, cannulation of the biliopancreatic system and prevention of endoscopic complications. Since there are no standardized practical and technical guidelines on this topic, this review illustrates these challenges with clinical cases.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) for endoscopic treatment of biliopancreatic disorders is performed with a side-viewing duodenoscope introduced through the mouth into the second portion of the duodenum, where the major (or minor) papilla is cannulated. It is a highly efficient technique combining both endoscopic and radiological imaging[1]. However, ERCP is prone to complications, even in experienced hands. Apart from bleeding, perforation, cholecystitis and cholangitis, post-ERCP pancreatitis is the most common[2]. There-

fore, it is considered an advanced endoscopy technique requiring specific training to perform sphincterotomy and sphincteroplasty, stone extraction, stent placement, tissue sampling and more[3].

However, additional difficulties and complications do arise when performing ERCP in postoperative patients with altered anatomy[4]. Proper knowledge of postoperative anatomy and training in conventional ERCP are mandatory before embarking into ERCP procedures in patients with surgically altered anatomy, as reviewed elsewhere[5,6]. In addition, when using device-assisted enteroscopy (DAE) to perform ERCP, training in deep enteroscopy is also necessary[4]. ERCP in patients with altered anatomy faces three important challenges determining the procedure's success rate: (1) ability to reach intact papilla of Vater or bilioenteric/pancreatoenteric anastomosis; (2) ability to cannulate intact papilla of Vater or bilioenteric/pancreatoenteric anastomosis; and (3) procedure-related complications. These topics will be highlighted in the current review.

Because of these difficulties, ERCP procedures in patients with altered anatomy are mostly performed in tertiary referral centers for advanced endoscopy, in close collaboration with the radiologist, surgeon and anesthesiologist. In order to correctly inform the patient about success rate and complication risks, it is advised to discuss these aspects in advance with the patient (and/or relatives), even if the patient is referred from another center. Finally, general anesthesia (with endotracheal intubation) is preferred for these demanding ERCP procedures.

Postoperative anatomy

Although recently reviewed and illustrated elsewhere, it is important to recapitulate the most prevalent surgical anatomy variations encountered during ERCP[4,5]. In general, currently encountered postoperative anatomy variations can be divided into: Billroth Ⅱ partial gastrectomy with intact papilla, short-limb Roux-en-Y reconstruction with intact papilla (total gastrectomy) or with bilioenteric/pancreatoenteric anastomosis (biliary diversion, Whipple resection) and long-limb Roux-en-Y reconstruction with intact papilla (gastric bypass, Scopinaro biliopancreatic diversion).

Endoscopes

Since there is no standardized procedure to perform ERCP in patients with altered anatomy and difficult-to-access biliopancreatic system, different types of endoscopes can be used, depending on local expertise and availability[4-6]. A conventional side-viewing duodenoscope can be used in a case of short-limb postoperative anatomy with variable success[5]. However, due to the difficult endoscopic orientation of a side-viewing endoscope in intestinal anastomoses with variable length limbs, the conventional duodenoscope carries important drawbacks in postoperative patients[7]. Therefore, alternative endoscopes have been used in order to increase the ERCP success rate[4]. Forward-viewing gastroscopes and colonoscopes, with or without additional distal cap, have been shown to be useful[5,8]. DAE (single-balloon, double-balloon and spiral enteroscopy) can also be used in the original long (200 cm) version or with an adapted shorter (152 cm) length[4-6,9-12]. Prototype endoscopes like the swan neck shaped multi-bending backward-oblique viewing duodenoscope (M-D scope, TJF-Y0011; Olympus)[13], the variable stiffness duodenoscope (TJF-Y0001; Olympus)[14] and the multi-bending forward-viewing endoscope with two working channels (M-scope, GIF-2T260M, Olympus)[15] may increase ERCP success rate in patients with altered anatomy[4].

FIRST CHALLENGE: HOW TO REACH INTACT PAPILLA OF VATER OR BILIOENTERIC/PANCREATOENTERIC ANASTOMOSIS?

In order to perform ERCP, the endoscope is positioned in front of the intact papilla of Vater or bilioenteric/pancreatoenteric anastomosis. In patients with surgically altered anatomy, intubation of the endoscope is more challenging, depending on the type of surgery. There are several critical steps determining the success rate of the intubation procedure. In patients with Billroth Ⅱ partial gastrectomy, the afferent limb is intubated through the gastrojejunostomy. However, the afferent limb is usually oriented on the right side of the anastomosis with a sharp angulation (Figure 1A). Crossing the anastomosis and angulation with a conventional side-viewing duodenoscope is difficult and increases the risk of perforation at the level of the anastomosis or the afferent limb[16]. Although the afferent limb is usually short (< 50 cm), its tortuous length may vary considerably, rendering complete intubation difficult. Forward-viewing endoscopes facilitate intubation of the afferent limb thanks to better endoscopic orientation during the intubation procedure[4,5]. In a case of a short-limb reconstruction, a conventional gastroscope can be used. However, sharp angulation at the level of the gastrojejunostomy or a long afferent limb may lead to loop formation in the gastric remnant, leading to failed intubation of the afferent limb (Figure 1B). Abdominal compression or changing the patient's position can be used to guide the endoscope[5]. Alternatively, the afferent limb may be differentiated (and marked with a submucosal tattoo) with a user-friendly gastroscope before switching to the duodenoscope[5]. Longer (variable stiffness) colonoscopes or DAE may overcome this difficulty[4]. However, the steerable tip of the colonoscope makes wider angulations compared to the gastroscope or enteroscope. The use of a semi-rigid overtube in a case of DAE inhibits loop formation of the enteroscope in the gastric remnant[10].

Postoperative Roux-en-Y anatomy is characterized by short (< 50 cm) or long (> 100 cm) limbs, depending on the type of surgery. Because of the lengthy limbs, longer endoscopes are usually necessary to reach the Roux-en-Y

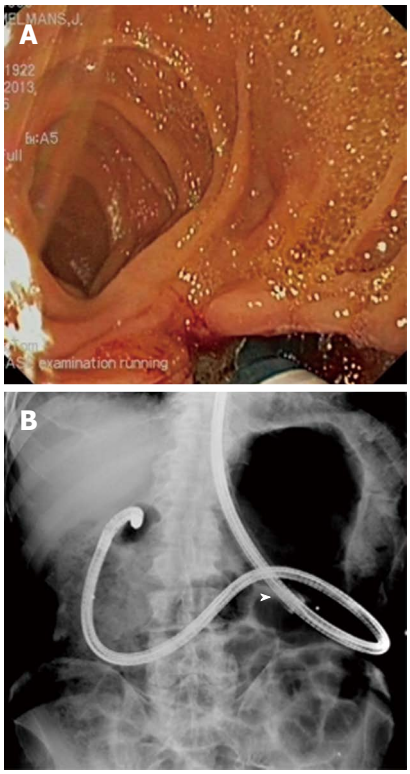

Figure 1 View Billroth Ⅱ. A: Endoscopic view of Billroth Ⅱ gastrojejunostomy with sharp angulation towards the afferent limb while retracting the single-balloon enteroscope. Note the mucosal tear at the short angle of the afferent limb at the end of the endoscopic retrograde cholangiopancreatography procedure; B: Radiological view of the looping position of the single-balloon enteroscope in the stomach of a patient with Billroth Ⅱ partial gastrectomy. The tip of the enteroscope is located in the blind end of the duodenum. The white arrow denotes the position of the deflated overtube balloon.

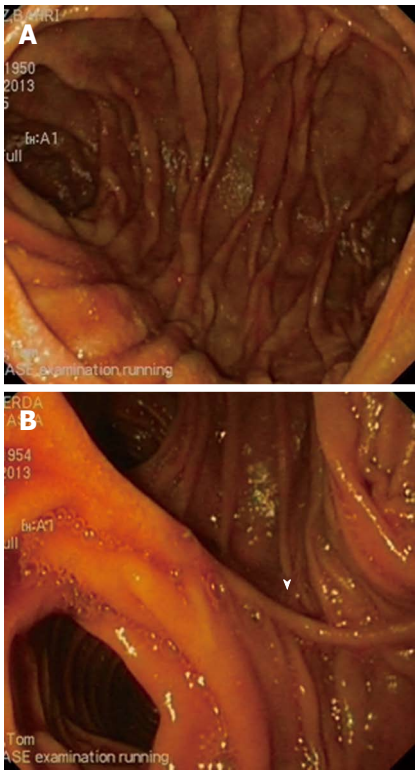

Figure 2 Endoscopic view of Roux-en-Y reconstruction. A: Endoscopic view of an end-to-side Roux-en-Y reconstruction with view on the afferent limb (right) and common limb (left). The white arrow denotes the operative scar of the anastomosis; B: Endoscopic view of a side-to-side Roux-en-Y reconstruction with view on the afferent limb (middle), common limb (left) and blind ending limb (right). The white arrow denotes the operative scar of the anastomosis.

anastomosis and to intubate the afferent limb. Since conventional duodenoscopes are not long enough, forward-viewing colonoscopes or DAE are used to perform ERCP in patients with Roux-en-Y reconstruction of the small bowel, with DAE being the most effective[4,5,17,18]. The first critical step is to reach the Roux-en-Y anastomosis through the alimentary limb, especially in a case of long-limb reconstruction. Ring-shaped metal surgical clips can sometimes be seen on fluoroscopy, identifying the location of the Roux-en-Y anastomosis, which is constructed either end-to-side or side-to-side (Figure 2). Identification of the afferent limb is challenging. To intubate the correct limb, the anastomotic scar must be crossed, avoiding the common limb towards the colon[6]. When done so, there are two remaining limbs in the case of a side-to-side reconstruction. One is short and ends blindly. The afferent limb can be recognized based on the presence of luminal bile and antiperistaltic motility. Similarly to the Billroth Ⅱ reconstruction, the angulation towards the afferent limb can be very sharp, leading to failed intubation. The use of a forward-viewing variable stiffness colonoscope or DAE with a semi-rigid overtube is mandatory in order to successfully intubate the afferent limb[4,5,17,19]. Sometimes abdominal compression may guide the endoscope into the right direction. Fluoroscopy is very helpful to identify the afferent limb since it is always heading towards the upper abdomen. When the endoscope heads down to the lower abdomen, it is located in the common limb.

Also, the afferent limb may be of considerable length and can be very torqued due to postoperative adhesions, posing a third critical step to reach the papilla or bilioenteric/pancreatoenteric anastomosis. Air enterogram by insufflation of a closed loop system helps to estimate the direction of the afferent limb and the distance towards the duodenum[11]. Until now, there appears to be no difference in efficacy in intubating the afferent limb between all three DAE methods (single-balloon, double-balloon, spiral enteroscopy)[18-20]. In addition, the short type single- and double-balloon enteroscopes are also effective to perform ERCP in patients with Roux-en-Y postoperative anatomy[9-12,21].

SECOND CHALLENGE: HOW TO CANNULATE INTACT PAPILLA OF VATER OR BILIOENTERIC/PANCREATOENTERIC ANASTOMOSIS?

In all cases of altered postoperative anatomy, the papilla or bilioenteric/pancreatoenteric anastomosis is reached

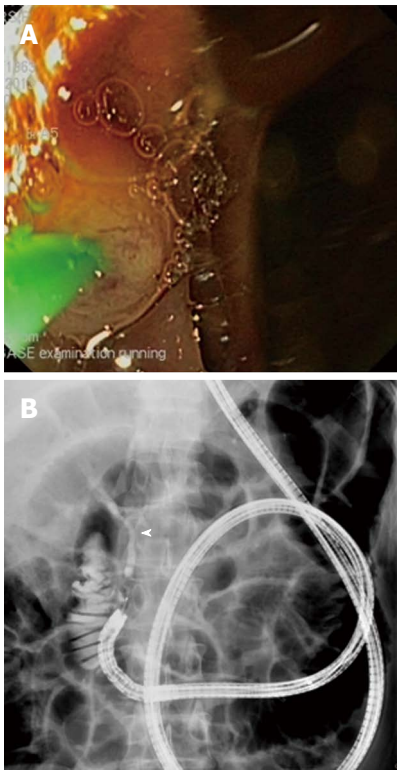

Figure 3 View. A: Endoscopic view of the distal approach to cannulate an intact papilla of Vater using a straight catheter with a forward-viewing endoscope. In order to cannulate in the direction of the common bile duct, the papilla is rotated into the 7 o'clock position; B: Radiological view of the double-balloon enteroscope in a patient with Roux-en-Y gastric bypass. The distal approach with a forward-viewing endoscope allows straight cannulation of the common bile duct (white arrow) in line with the direction of the working channel.

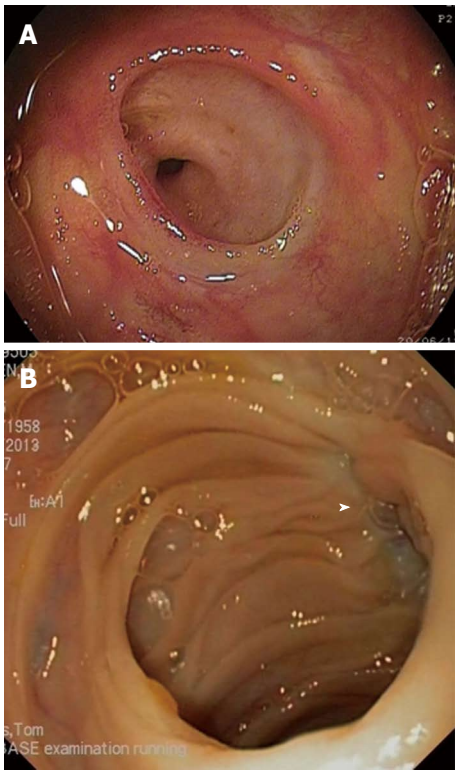

Figure 4 Endoscopic view of bilioenteric anastomosis. A: Endoscopic view of a normal end-to-side bilioenteric anastomosis; B: Endoscopic view of a stenosis at the level of the bilioenteric anastomosis. Only scar tissue (white arrow) indicates the location of the anastomosis without visible opening.

from below. This distal approach changes the direction of cannulation of papilla of Vater since the common bile duct is in direct line with the working channel of the forward-viewing endoscope, in contrast to conventional ERCP in normal anatomy using a side-viewing duodenoscope[6]. Unfortunately, this can be considered as the only advantage of the distal approach.

The first critical step to cannulate the intact papilla of Vater is the orientation of the endoscope. In contrast to conventional ERCP, the location of the papilla may be difficult, even when using a side-viewing duodenoscope in a Billroth Ⅱ gastrectomy patient[5]. Rotation of the endoscope is often necessary. This is the case even more with a forward-viewing gastroscope, colonoscope or DAE. Complete intubation of the endoscope up to the blind end of the afferent limb and then slow retraction until the papilla is in sight is probably the most efficient way to locate it. Then, rotation of the endoscope in order to face the papilla in the 7 o'clock position enables cannulation with a straight catheter, keeping in mind that the common bile duct is thus in line with the working channel of the forward-viewing endoscope (Figure 3)[6]. However, unstable endoscope position and the lack of a forceps elevator modality renders cannulation challenging. A distal cap at the tip of the forward-viewing endoscope may help cannulation since it enables tilting of the papilla[8]. In general, it is easier to cannulate the common bile duct from the distal approach with a forward-viewing endoscope compared to the pancreatic duct.

There is considerable advantage of cannulation of a bilioenteric/pancreatoenteric anastomosis over cannulation of an intact papilla because of the lack of a sphincter in a papillary structure. This results in higher ERCP success rates[22-24]. Classical end-to-side bilioenteric anastomosis can be clearly identified as a hole in the wall of the afferent limb (Figure 4A). Its presence and location can be identified by means of intermittent bile flow in the afferent limb. However, when stenosis occurs at the level of the bilioenteric or pancreatoenteric anastomosis, its location is difficult and should be identified with the help of fluoroscopy, showing the position of the endoscope's tip near the liver or the pancreas. Air cholangiogram with insufflation of the closed afferent limb may locate the open bilioenteric anastomosis. Otherwise, mucosal scar tissue with star shaped folds may direct to the location of the strictured anastomosis (Figure 4B).

One has to take into account that using DAE for ERCP necessitates adapted specialized accessory catheters because of the length (230 cm) and the diameter (2.8 mm) of the working channel of currently used enteroscopes[4-6]. Conventional ERCP catheters can therefore not be used with these enteroscopes. Moreover, plastic stent placement is only possible with 5 or 7 Fr stents and not with the conventionally used 10 Fr stents. Self-expandable metal biliary or pancreatic stents cannot be used

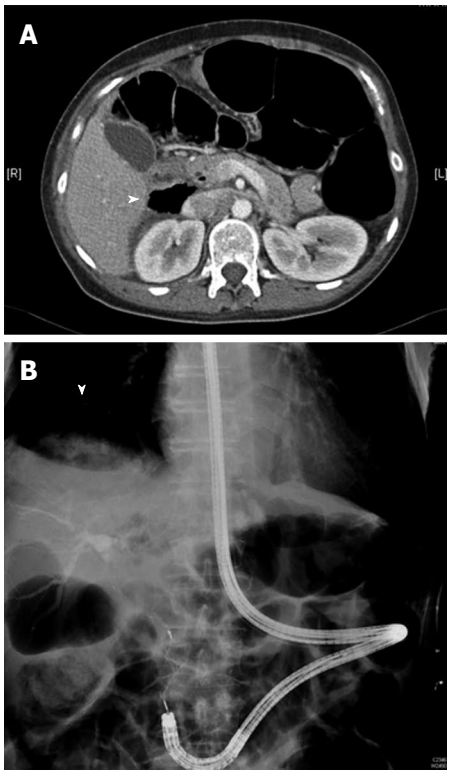

Figure 5 A patient with Roux-en-Y gastric bypass. A: Computed tomography of a retroperitoneal perforation (white arrow) at the level of papilla of Vater after sphincterotomy and sphincteroplasty in a patient with Roux-en-Y gastric bypass; B: Radiological view of hepatic capsule dehiscence without free abdominal air (white arrow) due to barotrauma in the closed afferent limb during single-balloon enteroscopy endoscopic retrograde cholangiopancreatography in a patient with Billroth Ⅱ partial gastrectomy. Common bile duct stone retrieval with a basket is being performed.

with enteroscopes because of the length and diameter mismatch of the working channel. Alternative procedures with a percutaneous or laparoscopy-assisted approach are mandatory when metal stent placement is required, as reviewed elsewhere[4,5].

THIRD CHALLENGE: HOW TO AVOID COMPLICATIONS?

A review of the literature demonstrates a complication risk ranging from 0% to 19.5% of ERCP procedures in patients with altered anatomy, with perforation being the most frequent and sometimes lethal, followed by bleeding, cholangitis, mucosal tears and post-ERCP pancreatitis[6]. The risk of post-ERCP pancreatitis remains relatively low, in contrast to conventional ERCP, since most indications for ERCP in patients with altered anatomy are restricted to the biliary tract, which is more easily cannulated in the distal approach compared to the pancreatic duct[2,6].

Intestinal perforations may occur at different levels along the intubated tract, leading to abdominal, retroperitoneal or subcutaneous free air[6]. ERCP in the early postoperative phase should be avoided in order not to disrupt fresh surgical anastomoses[23]. Difficult intubation across sharply angulated anastomoses or postoperatively fixed and torqued intestinal limbs may lead to perforation along the intestinal tract. At the level of the papilla, perforation may occur after sphincterotomy and/or sphincteroplasty due to a less well-controlled cutting procedure with a forward-viewing endoscope in an unstable position.

Finally, a peculiar barotrauma in a closed loop system may occur when intraluminal pressure increases steadily in the blind afferent limb. This may occur when using balloon-assisted enteroscopy overtubes sealing the distal end of the blind afferent limb. When air is insufflated continuously during the procedure without the ability to decompress via mouth or anus, intraluminal pressure increases in the closed afferent limb, resulting in air leakage through a wall weakness (sphincterotomy, mucosal tear in afferent limb, biliary tract after sphincterotomy/sphincteroplasty) (Figure 5). This risk is lower in gastric bypass patients since the insufflated air can escape into the excluded stomach which can still dilate and decompress the afferent intestinal limb. However, in all other surgical variations, this risk is present when performing single- or double-balloon enteroscopy ERCP. Another type of barotrauma can be seen during direct cholangioscopy using a slim forward-viewing endoscope. After sphincterotomy and additional sphincteroplasty, the forward viewing gastroscope, pediatric colonoscope or enteroscope can be introduced into the common bile duct since it is direct in line with the endoscope. Continuous air insufflation into the closed biliary tract may cause rupture of the gallbladder or dehiscence of the hepatic capsule (Figure 6). These types of barotraumas should be avoided by using CO_2-insufflation which is absorbed much faster by the intestinal mucosa compared to air and intermittent desufflation of the overtube's balloon in order to allow decompression of the afferent limb. This maneuver of balloon desufflation may lead to position loss of the enteroscope and the need for re-introduction.

CONCLUSION

ERCP in patients with altered anatomy remains a challenging procedure. Technical difficulties defined by inability to reach or to cannulate the biliopancreatic system and complications determine the overall success rate of these advanced endoscopic procedures. The availability of new types of endoscopes nowadays allows ERCP in patients with altered anatomy, even with long-limb Roux-en-Y reconstruction. However, the use of these new endoscopes may lead to new difficulties and complications like previously unseen barotraumas in closed afferent intestinal limbs. There is currently no gold standard approach to deal with biliopancreatic disorders in patients with surgically altered anatomy. In addition, there are no standardized technical guidelines available since ERCP in patients with altered anatomy is an endoscopic procedure in active evolution, aiming for faster, easier, more effi-

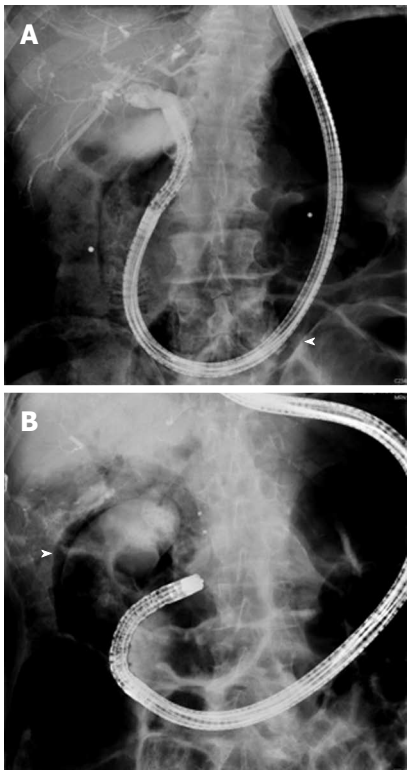

Figure 6 Radiological view. A: Radiological view of direct cholangioscopy with the single-balloon enteroscope inside the common bile duct and with the overtube (white arrow) inside the afferent limb of a Billroth Ⅱ patient; B: Radiological view of free air around the contrast-filled gallbladder (white arrow) due to barotrauma during single-balloon enteroscopy endoscopic retrograde cholangiopancreatography in a Billroth Ⅱ patient.

cient and safer results.

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RETROSPECTIVE STUDY

Continued evidence for safety of endoscopic retrograde cholangiopancreatography during pregnancy

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Abstract

AIM: To report the safety of continued use of endoscopic retrograde cholangiopancreatography (ERCP) during pregnancy at various maternal ages.

METHODS: A retrospective chart review of pregnant patients who underwent ERCP at a tertiary academic center was undertaken between 2002 and 2012. Pertinent past medical history and initial presenting laboratory data were collected. Review of the procedure note for each ERCP performed provided documentation of lead shielding, type of sedation, fluoroscopy time, and post-procedure complications. Patients' clinical courses were reviewed until the time of delivery and pregnancy complications with fetal outcomes were examined. Data was stratified based upon the mother's age at the time of ERCP: 18-21, 22-29, and ⩾ 30 years of age.

RESULTS: Twenty pregnant patients who underwent ERCP between 2002 and 2012 were identified. The mean age at the time of ERCP was 26.4 years (18-38 years) and the average trimester was the second. The indications for ERCP were choledocholithiasis in 17 patients, gallstone pancreatitis in 2 patients, and cholangitis in 1 patient. The mean fluoroscopy time of ERCP was 3.8 min (0.3-23.6 min). Sphincterotomy was performed in 18 patients with therapeutic intent and not as a prophylactic measure to prevent recurrences. Clinical documentation of use of protective shielding was found in only 8 notes (40%). Post procedure complications were limited to two cases of post-ERCP pancreatitis (10%). Elective cholecystectomy was performed shortly after ERCP in 11 of the pregnant patients. Birth records were available for 16 patients, of which 15 had full-term pregnancies. Cesarean sections were performed in 5 (31%) patients. Term birth weight was greater than 2500 g in all cases except one in which the mother had a known hypercoagulable state.

CONCLUSION: ERCP during pregnancy is both safe and efficacious regardless of maternal age or trimester.

Key words: Endoscopic retrograde cholangiopancreatography; Pregnancy; Choledocholithiasis; Pancreatitis; Cholecystectomy; Caesarean section

Core tip: The incidence of choledocholithiasis during pregnancy has been estimated to be 1 in 1000. Although Endoscopic retrograde cholangiopancreatography (ERCP) remains the gold standard for treatment of symptomatic choledocholithiasis during pregnancy, there still remain safety concerns about it use. Women who conceive at "extremes of age" are at an increased risk for complications during pregnancy. Our study supports the safety and efficacy of ERCP during the peripartum period for both mothers and their newborns. Neither advanced age nor trimester in which the pro-

cedure was performed carried a higher risk for adverse outcomes during pregnancy.

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INTRODUCTION

Pregnancy carries an increased risk for gallstone formation. Hormonal changes lead to imbalances of bile composition and secretion. Estrogen is thought to increase cholesterol secretion leading to supersaturation, while progesterone both decreases bile acid secretion and gallbladder motility[1]. Studies have shown increasing amounts of biliary sludge with trimester[2] with a rate of gallstone formation to occur in up to 12% of pregnant women[3]. It is estimated that 1 in 1000 pregnancies are complicated by choledocholithiasis[4]. Immediate and safe intervention in symptomatic choledocholithiasis has proven to be vital in preventing life-threatening outcomes to both the mother and fetus. Endoscopic retrograde cholangiopancreatography (ERCP) is currently the gold standard to treat choledoscholithiasis[5]. However, there continues to be expected concern around the procedure in regards to safety of radiation exposure to the pregnant patient and unborn fetus. Furthermore, women at "extremes of maternal age" have been shown to have different risk profiles during pregnancy; young women carry a higher risk for pre-term delivery while older women are more prone to cesarean section or offspring requiring neonatal unit admission[6]. We therefore investigated the safety of ERCP during pregnancy and outcomes in regards the patient's age during which the procedure was performed.

In this single center study we report our experience with 20 pregnant patients who underwent therapeutic ERCP by experienced endoscopist.

MATERIALS AND METHODS

Patient population

The patient's history, laboratory data, hospital course, ERCP procedure, and delivery/fetal outcomes were obtained through chart review through both Rhode Island and Women and Infants Hospitals. The study was approved by both hospitals Institutional Review Board. We divided the patients into three different groups based on what has previously been performed in obstetric studies investigating outcomes/adverse events in regards to age[6]. Given the limited number of patients, we created three age brackets based on the age of the patient at the time of the ERCP procedure; teens to young twenties (18-21), mid-upper twenties (22-29), and $\geqslant$ 30 years old.

Term pregnancy was considered to be equal to or greater than 37 wk at time of delivery. Trimesters where broken down into the following: first trimester weeks 1-14, second trimester weeks 15-28 and third trimester weeks greater than or equal to 29. Small for gestational age when baby's weight was less than 2500 g at delivery. Apgar scores at 5 min were used as data points, considering a score of 7 or above to be normal. Lastly, any documentation of birth defects was also noted. In regards to the maternal adverse events, documentation of post-procedure or antenatal complications was reported when available.

All laboratory data used in this study were values collected on initial presentation to the hospital. A skilled endoscopist performed all ERCPs with a therapeutic intent based on abnormal abdominal ultrasound or magnetic resonance cholangiopancreatigraphy (MRCP).

Endoscopic procedure

ERCP was performed with the patient lying in the left lateral decubitus position. Standard maternal monitoring during the procedure took place largely by an endoscopy nurse or by anesthesiologist if monitored anesthesia care (MAC) was administered. Sedation was largely achieved through the use of conscious sedation using combinations of intravenous fentanyl, midazolam, or meperidine. In 3 cases, an anesthesiologist administered MAC. Continuous fetal monitoring was performed by a delivery nurse on all patients at 24 wk of gestation or later. Standard practice during the procedure was that the gravid pelvis was shielded using a lead drape to limit radiation exposure to the fetus. Biliary cannulation was achieved by using a sphincterotome and was confirmed by aspiration of bile. Contrast cholangiogram was performed to visualize the presence of stones/obstruction and removal was accomplished by either balloon or retrieval basket. Sphincterotomy, when indicated, was performed by a monofilament short-tip traction sphincterotome using blended current. If indicated, plastic stents were placed. In cases of mild post sphincterotomy bleeding, epinephrine was injected or tamponade performed. Lastly, the diagnosis of post-ERCP pancreatitis consisted of the combination of abdominal pain and elevated lipase.

Statistical analysis

This study used descriptive statistics to compare the different findings of the study. The data collected was pooled into corresponding age groups and presented as whole numbers followed by (%) or as means followed by the standard deviation (SD).

RESULTS

Study population

Twenty pregnant patients were identified between 2002-2012. Five patients were Caucasian, six were African American, and nine of other ethnicities. The mean age of all patients at the tine of procedure was 26.4 years (18-38

Table 1 Baseline characteristics and laboratory data

	All patients (n = 20)	Age 18-21 (n = 7)	Age 22-29 (n = 8)	Age ⩾ 30 (n = 5)
Age (yr)	26.4 (6.18)	20.1 (1.21)	26.5 (2.26)	35 (3.08)
Race (Caucasian/African American/other)	5/6/9	0/2/5	2/3/3	3/1/1
Parity	2.25 (1.16)	1.42 (0.78)	3 (0.92)	2.2 (1.3)
Past medical history				
Hypertension	2	0	1	1
Hypothyroidism	1	0	1	0
History of latent tuberculosis	2	0	2	0
Depression	4	2	2	0
Asthma	1	0	1	0
Coagulopathy	1	0	0	1
Prior hepatitis B infection	2	1	0	1
Reflux disease	1	1	0	0
History of gallbladder disease	6	1	3	2
White blood cell (4.0-11.0 x 10^9/L)	8.6 (2.28)	8.42 (2.54)	9.61 (2.53)	7.54 (1)
Hemoglobin (11.7-16 g/L)	12 (1.29)	11.9 (0.88)	11.8 (1.93)	12.32 (0.23)
Platelet count (150-440 x 10^9/L)	261.1 (62.63)	263.1 (62.6)	255 (75.9)	267.2 (50.32)
AST (20-30 units/L)	163 (111.38)	127.4 (100.3)	162.1 (129.8)	214.2 (93.8)
ALT (5-32 units/L)	213.5 (214)	183.4 (165.3)	228.8 (299.7)	231 (135.5)
Total bilirubin (0.1-1.1 mg/dL)	2.6 (1.9)	2.84 (2.37)	2.36 (1.68)	2.64 (1.99)
Alkaline phosphatase (16-100 units/L)	189.1 (96)	162.8 (39.2)	223 (142.2)	171.6 (47.36)
Lipase (4-57 units/L)	1105 (1736.5)	519.7 (1258)	1669 (2104)	1025 (1719.2)

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

years). Eight patients were in the age bracket 18-21, seven in 22-29, and five ⩾ 30 years old. The past medical history, parity, and initial presenting laboratory data were collected for each of the patients on admission and were then separated based on specific age groups (Table 1).

Indication/preventative measures/procedure outcomes

All ERCPs were performed with a therapeutic intent. The mean trimester at which ERCP was performed was in the second. The indications for ERCP were choledocholithiasis in 17 patients, gallstone pancreatitis in 2 patients, and cholangitis in 1 patient. (Table 2). The overall mean fluoroscopy time during ERCP was 3.8 min (Range: 0.4-23.6 min). The mean fluoroscopy times with respected ranges in parenthesis for the different age groups were: 6.5 min (0.4-23.6 min) Age 18-21, 2.2 min (0.4-9.1 min) Age 22-29, and 2.7 min (0.3-7.6 min) for ⩾ 30 years (Table 2). Eighteen patients (90%) had biliary sphincterotomy performed during ERCP. Of the 2 remaining cases, sphincterotomy was not performed because one patient was noted to have had a prior sphincterotomy and the second patient had a normal cholangiogram. Four (20%) patients had plastic stents placed. The indication for stent placement in 3 cases was evidence of pus and to allow for ample drainage, while the last stent was placed due to prolonged procedure time (23.6 min) with an inability to completely remove the stone. Five (25%) patients were noted to have two or more stones removed from the common bile duct at the time of procedure (Table 2). Lastly, our clinical practice refers patients to a general surgeon for elective cholecystectomy after evidence of biliary obstruction and resolution with ERCP. Three (15%) patients had a prior history cholecystectomy being performed. Eleven (55%) patients had documented cholecystectomy after having had ERCP, while six (30%) patients had no record of having the follow-up procedure (Table 2).

Sedation/procedure complications/antibiotic use

Seventeen patients received conscious sedation that consisted of a combination of midazolam with either fentanyl or meperidine. In the other 3 cases, MAC was administered. Regardless of the type of sedation used, there were no observed complications in regard to maternal or fetal well being. Though it was common practice in our endoscopy suite to use lead shielding to the pelvis and optimal positioning, there were only 8 (40%) instances of these preventative practices being documented in the procedure note. Post procedure complications in our patient population were limited to 2 (10%) cases of post-ERCP pancreatitis and both patients were noted to have multiple stones on ERCP (Table 2). Minor post sphincterotomy bleeding was seen in 2 cases (10%). Bleeding in both cases was controlled by either balloon tamponade or epinephrine injection at the site. Lastly, Piperacillin/Tazobactam was administered post-ERCP in 2 cases for either frank pus or suspected infectious debris post clearance of the common bile duct.

Fetal outcome

Birth records were available for 16 (80%) patients (Table 3). In each of the three different age groups, one patient's follow-up was lost due to delivery at an outside hospital. The additional patient, in the age group 22-29, had an elective termination of the pregnancy. Term pregnancy was seen in 15 (93%) patients. Cesarean sections were performed in 16% of patients in age brackets 18-21 and 22-29, while 75% of patients in the age bracket ⩾ 30 had

Table 2 Endoscopic retrograde cholangiopancreatography indications, outcomes, and complications

	All patients (n = 20)	Age 18-21 (n = 7)	Age 22-29 (n = 8)	Age ⩾ 30 (n = 5)
Trimester	2 (0.77)	2.14 (0.89)	2 (0.92)	1.8 (0.44)
Indication for ERCP				
Common bile duct stone	17	5	8	4
Gallstone pancreatitis	2	2	0	0
Cholangitis	1	0	0	1
Protective shielding stated in note	8	3	1	4
Anesthesia				
Midazolam	17	6	7	4
Fentanyl	5	2	3	0
Propofol	3	1	1	1
Meperidine	13	4	5	4
Fluoroscopy dose/min	3.8 (5.5)	6.5 (8.5)	2.2 (2.8)	2.7 (3.0)
Spot radiographs	6	2	3	1
Sphincterotomy	18	5	8	5
Stenting	4	2	1	1
2 ⩾ stones removed	5	1	1	3
Post ERCP antibiotic				
Piperacillin/tazobactam	2	0	1	1
Post-ERCP complications				
Pancreatitis	2	1	1	0
Oversedation	0	0	0	0
Perforation	0	0	0	0
Cholangitis	0	0	0	0
Contrast dye reaction	0	0	0	0
Bleeding	2	1	1	0
Cholecystectomy				
Prior history of receiving	3	0	1	2
Post ERCP	11	5	5	1

ERCP: Endoscopic retrograde cholangiopancreatography.

Table 3 Pregnancy outcomes

	All patients (n = 16)	Age 18-21 (n = 6)	Age 22-29 (n = 6)	Age ⩾ 30 (n = 4)
Term pregnancy	15	6	6	3
Caesarean section	5	1	1	3
5 min Apgar score	8.77 (0.73)	9 (0)	9 (0)	8 (1.4)
Birth weight in grams	2638 (1227)	3200 (472)	3297 (408.8)	2838 (883)
Fetal malformations	1	0	0	1

a C-section. Term birth weight was greater than 2500 g in all cases except for one which also had a cleft palate. This was attributed to the mother's significant history for clotting disorder, which had resulted in cerebral vein thrombosis in the past. This pregnancy was noted for severe intrauterine growth restriction and required induced cesarean section delivery at 36 wk. Examination of the placenta revealed extensive chronic vilitis, avascular vili, and 30% of infarcted placenta. Apgar scores at 5 min were all 9, except for one score of 6 in the offspring of the patient with a known clotting disorder and required the Neonatal Intensive Care Unit (NICU) admission after birth.

DISCUSSION

In our study, we further expound on the continued evidence for safety of ERCP during pregnancy. When management of pregnant patients with biliary tract disease can no longer be safely managed conservatively, ERCP still proves to be an invaluable therapeutic tool for maintaining a viable pregnancy. The concern has largely focused on the fetal-radiation exposure and outcomes the procedure may have on pregnancy. The limited data of reported outcomes for ERCP during pregnancy in the current literature continues to be a barrier of comfort for even the experienced proceduralist. Although our study is limited by the number of study subjects, it nevertheless contributes to the growing body of literature that supports the continued safety of ERCP during pregnancy.

Women who conceive at a later age are at an increased risk for complications during pregnancy[7]. Advanced age carries an increased risk for spontaneous abortion, likely due to decline of oocyte quality[8]. Coexisting medical conditions such as hypertension and diabetes are more prevalent with increasing age leading to further risk during pregnancy. Older age has also been associated with increased rates of low birth weight[9], the use of cesarean delivery[10], increased risk of stillbirth[11], as well as heightened pregnancy related maternal mortality[12]. Conversely, younger pregnant patients are more likely to be underweight, smoke, and have a higher risk for preterm birth[6]. The different age brackets of pregnant patients in our study did not show increased rates of spontaneous abortion, low birth rate, preterm delivery, or maternal death. One patient who was of advanced age with a significant history for pro-thrombotic state was the only patient noted to have complications requiring induction and preterm delivery due to severe low intrauterine growth

restriction and a birth weight less than 2500 g requiring NICU admission. On further analysis of the placenta she was noted to have 30% of the placental area that was infracted, suggesting the cause of complications was due to her clotting history. Of note, the first two age brackets (18-21 and 22-29) had equivalent rates of C-section, 16%. However, in the age group ≥ 30, 75% of the patients gave birth *via* C-section. We suspect that this is largely due to the already reported trend of increased rates of delivery *via* cesarean section with advancing age[6,10] and not as a result from intervention with ERCP.

Fetal radiation exposure during ERCP still remains a valid concern for the pregnant patient. Radiation exposure has been linked to congenital malformations, growth retardation, fetal death, and childhood cancer[13]. Ionizing radiation is measured in rads (radiation absorbed dose). The level that is considered to be teratogenic is between 5-10 rads[14]. The use of hard films during ERCP procedure can also be a source of radiation exposure to the fetus. The mean fluoroscopy time in our study was 3.8 min (Range: 0.3-23.6 min) that corresponded to an calculated estimated uterine dose of about 1.18 rads, well below the level of concern for teratogenic effect[15]. Furthermore, six of the patients had spot radiographs taken during the procedure. Two patients had greater than five films taken; one 7 and the other 11 and both with long fluoroscopy times of 9.1 min and 10.8 min respectively. Both patients were in the first trimester at the time of the procedure and neither pregnancy had complications documented. Efforts have been made to eliminate the need for fluoroscopy during ERCP that have relied on aspiration of bile after canulation to confirm the location[16,17]. Fluoroscopy provides the ability to confirm complete removal of all stones and debris. This decreases the need for repeat procedures and unnecessary risk to the mother and fetus[18]. Furthermore, Smith *et al*[19] demonstrated that routine ERCP has minimal radiation exposure to the fetus and that measurement with thermoluminescent dosimeters does not appear to be necessary.

Proper positioning and shielding of the unborn fetus help to further limit radiation exposure. Having the patient in the left lateral decubitus position allows for optimal blood by limiting compression of the inferior vena cava and aorta by the gravid uterus[20]. Lead shielding to the uterus helps to minimize radiation exposure along with minimized procedure time. Though it was standard practice of our endoscopy unit to perform these maneuvers, documentation of these being done was found in only 40% of the procedure notes. In this era of computerized medical records, careful documentation of these preventative interventions in pregnant patients is prudent and should not be overlooked.

Performing prophylactic sphincterotomy after a normal cholangiogram is controversial. Barthel *et al*[21] performed biliary sphincterotomy in 3 patients who presented with gallstone pancreatitis and reported healthy pregnancies with no further recurrences of pancreatitis, despite no evidence of choledocholithiasis on ERCP. Tang *et al*[22] also showed that sphincterotomy could successfully reduce recurrent pancreatitis. Though this study had high rates of sphincterotomy being performed, half of the patients who received them were also noted to have choledocholithiasis which justified its use. Prophylactic sphincterotomy can lead to biliary bacterial colonization, duodenal reflux, and may increase the risk of post-ERCP pancreatitis. In our study, sphincterotomy was only performed when clinically indicated for stone removal and was not used for prophylactic measures. Furthermore, referral to a general surgeon for elective cholecystectomy shortly after ERCP appears to be safe and does not carry a higher risk for morbidity when compared to non-pregnant patients[23]. Eleven (55%) patients had documentation of a successful cholecystectomy later on during pregnancy in our study. Heightened awareness for the safety of cholecystectomy after therapeutic ERCP, as a preventative solution to future stone complications during pregnancy, appears to be a more favorable treatment solution.

Complications of ERCP can consist of acute pancreatitis, hemorrhage, and even perforation. In prior studies, the estimated rates of post-ERCP pancreatitis have ranged from 2.6% to 15.1%[24,25]. In our study, we had 2 (10%) cases of post-ERCP pancreatitis based on the clinical exam findings and laboratory values. Our pancreatitis occurrence rate falls in between previously reported expected study rates. Both cases were mild and resolved with supportive care. ERCP during pregnancy does not carry a higher incidence rate of pancreatitis than in the general population.

The long-term effects of ERCP on offspring have not been closely studied. This is largely due to the disconnection between the endoscopist and unborn child, as well as the difficulty of following newborns prospectively. Gupta *et al*[26] followed 11 out of 18 children for a median of 6 years post-procedure. All subjects were reported to be healthy without congenital or developmental complications. This small but important study confirms our notion that when prophylactic measures are taken to limit radiation exposure during ERCP, there seem to be no adverse effects on the developing child. However, continuing to follow children overtime with the help of their pediatricians would allow for longer observation and further confirmation of our current conceived notions.

In conclusion, our study supports the safety and efficacy of ERCP during the peripartum period for both mothers and their newborns. ERCP intervention in regards to different age brackets did not appear to confer higher risk to the pregnancy than what is already reported in the literature. Rates of C-Section appear to be more prevalent with aging patients and not as a result of having ERCP during gestation. Pregnant women who had ERCP performed are also not at a higher risk for post-ERCP pancreatitis than the general population. A skilled and well-versed endoscopist is needed in order to therapeutically intervene as well as minimizing fetal radiation. Although there appears to be no long-term effects on children, further data collection needs to continue to reaffirm this. ERCP during pregnancy should include a

multi-disciplinary team approach to ensure the safety and well being of both the mother and offspring.

COMMENTS

Background

Pancreaticobiliary disease during pregnancy is not only common, but may also increase the risk of peripartum complications. Therapeutic endoscopic retrograde cholangiopancreatography (ERCP) remains the gold standard for treatment of symptomatic choledocholithiasis with or without pregnancy. However, there still remain concerns about the safety of its continued use during pregnancy with regards to both the mother and unborn fetus.

Research frontiers

Modifications to ERCP during pregnancy have been proposed in an attempt to reduce the use of radiation that may have long-term consequences on the fetus. However, these measures that do not employ fluoroscopy do not afford the same diagnostic and therapeutic yield. Continued reporting of the safety of ERCP with fluoroscopy in pregnancy allows both providers and pregnant patients to have confidence that they may safely and appropriately treat biliary disease.

Innovations and breakthroughs

Prior studies have reported safety data by trimester of pregnancy when ERCP was performed. Conversely, this study divided groups based upon the mother's age at the time of the intervention. Extremes of maternal age may portend an elevated risk of peripartum complications. However, this study did not demonstrate that a specific maternal age bracket carried an increased risk for peripartum adverse events secondary to ERCP intervention.

Applications

These data add to existing literature that ERCP during pregnancy is safe for both the mother and fetus. Furthermore, the patient's age at the time of the procedure does not significantly impact the risk of adverse peripartum events.

Terminology

Protective lead shielding and left lateral decubitus positioning of the patient were standard measures taken to limit radiation exposure and fetal distress.

Peer review

This is an interesting study that has been presented in a clear, well-written manuscript.

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RETROSPECTIVE STUDY

Virtual chromoendoscopy in small bowel capsule endoscopy: New light or a cast of shadow?

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Abstract

AIM: To evaluate whether virtual chromoendoscopy can improve the delineation of small bowel lesions previously detected by conventional white light small bowel capsule endoscopy (SBCE).

METHODS: Retrospective single center study. One hundred lesions selected from forty-nine consecutive conventional white light SBCE (SBCE-WL) examinations were included. Lesions were reviewed at three Flexible Spectral Imaging Color Enhancement (FICE) settings and Blue Filter (BF) by two gastroenterologists with experience in SBCE, blinded to each other's findings, who ranked the quality of delineation as better, equivalent or worse than conventional SBCE-WL. Inter-observer percentage of agreement was determined and analyzed with Fleiss Kappa (κ) coefficient. Lesions selected for the study included angioectasias (*n* = 39), ulcers/erosions (*n* = 49) and villous edema/atrophy (*n* = 12).

RESULTS: Overall, the delineation of lesions was improved in 77% of cases with FICE 1, 74% with FICE 2, 41% with FICE 3 and 39% with the BF, with a percentage of agreement between investigators of 89% (κ = 0.833), 85% (κ = 0.764), 66% (κ = 0.486) and 79% (κ = 0.593), respectively. FICE 1 improved the delineation of 97.4% of angioectasias, 63.3% of ulcers/erosions and 66.7% of villous edema/atrophy with a percentage of agreement of 97.4% (κ = 0.910), 81.6% (κ = 0.714) and 91.7% (κ = 0.815), respectively. FICE 2 improved the delineation of 97.4% of angioectasias, 57.1% of ulcers/erosions and 66.7% of villous edema/atrophy, with a percentage of agreement of 89.7% (κ = 0.802), 79,6% (κ = 0.703) and 91.7% (κ = 0.815), respectively. FICE 3 improved the delineation of 46.2% of angioectasias, 24.5% of ulcers/erosions and none of the cases of villous edema/atrophy, with a percentage of agreement of 53.8% [κ = not available (NA)], 75.5% (κ = NA) and 66.7% (κ = 0.304), respectively. The BF improved the delineation of 15.4% of angioectasias, 61.2% of ulcers/erosions and 25% of villous edema/atrophy, with a percentage of agreement of 76.9% (κ = 0.558), 81.6% (κ = 0.570) and 25.0% (κ = NA), respectively.

CONCLUSION: Virtual chromoendoscopy can improve the delineation of angioectasias, ulcers/erosions and villous edema/atrophy detected by SBCE, with almost perfect interobserver agreement for FICE 1.

Key words: Capsule endoscopy; Virtual chromoendoscopy; Small bowel enteroscopy; Flexible Spectral Imag-

ing Color Enhancement Endoscopy; Imaging review

Core tip: One of the recent technical advances of small bowel capsule endoscopy (SBCE) technology is the possibility to enhance endoscopic imaging with computed virtual chromoendoscopy, using the Flexible Spectral Imaging Color Enhancement (FICE) or the Blue Filter modes. In our study, virtual chromoendoscopy, particularly FICE 1, improved the delineation of three main types of small bowel mucosal lesions: vascular (angioectasias), mucosal breaks (ulcers and erosions) and villous pattern (edema and atrophy), with substantial inter-observer agreement. Thus, we support the use of virtual chromoendoscopy as a complement to conventional white light SBCE for the evaluation of difficult to interpret endoscopic images.

Cotter J, Magalhães J, Dias de Castro F, Barbosa M, Boal Carvalho P, Leite S, Moreira MJ, Rosa B. Virtual chromoendoscopy in small bowel capsule endoscopy: New light or a cast of shadow? *World J Gastrointest Endosc* 2014; 6(8): 359-365 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i8/359.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i8.359

INTRODUCTION

Small bowel capsule endoscopy (SBCE) is a well established diagnostic procedure for the evaluation of small bowel diseases, with a high diagnostic yield when compared to other small bowel imaging modalities[1-5]. Recently, SBCE diagnostic abilities have been further expanded with the incorporation of virtual chromoendoscopy into the versions 6, 7 and 8 of RAPID® Reader (Given® Imaging Ltd, Yoqneam, Israel)[6-8], using the Flexible Spectral Imaging Color Enhancement (FICE, Fujinon Corporation®, Saitama, Japan) and the Blue Filter (BF). FICE uses a spectral estimation technology, narrowing the bandwidth of white light that permits an automatic reconstruction of pre-acquired conventional endoscopic images into virtual images with different wavelengths of red, green and blue, in order to enhance vascular contrast and the resolution of surface patterns[9,10]. The BF is another setting of virtual chromoendoscopy consisting of colour enhancement within a short wavelength range (490-430 nm). Virtual chromoendoscopy works with the convenience of a quick push-button switch between white light and chromoendoscopy with no need for dye spraying[11]. Virtual chromoendoscopy has been extensively investigated in the upper and lower GI tract[9,12-14], and recently in double-balloon enteroscopy[15]. Despite the conflicting data, most studies support its use to improve the evaluation of size, borders and mucosal pattern of different types of lesions[9,11,16-18]. However, it is currently controversial whether virtual chromoendoscopy may increase the diagnostic yield and diagnostic accuracy of SBCE, and what are the optimal wavelength filters to be used[7,11,19].

The aim of this study was to evaluate whether the currently available virtual chromoendoscopy settings may improve the delineation of the most frequent small bowel mucosal lesions detected by conventional white light SBCE (SBCE-WL).

MATERIALS AND METHODS

Type of study and selection of participants

We conducted a retrospective single center study, which included forty nine consecutive SBCE examinations for the investigation of patients with iron deficiency anemia, overt or occult obscure digestive bleeding and suspected or known Crohn's disease.

Procedures

All patients followed a 24 h clear liquid diet and 12 h fasting prior to SBCE (PillCam® SB, Given® Imaging Ltd Yoqneam, Israel). No oral purge was administered. All videos were reviewed with conventional white light by a gastroenterologist with extensive experience on SBCE (> 500 procedures), who selected 100 consecutive lesions to enter the study, including vascular lesions (angioectasias, $n = 39$), mucosal breaks (ulcers/erosions, $n = 49$) and villous morphology changes (villous edema/atrophy, $n = 12$) (Figure 1). All lesions were described using the terminology proposed by the Given Capsule Endoscopy working group[20]. According to the methodology of the study, two gastroenterologists with experience in SBCE (more than 200 examinations) reviewed the selected lesions using all three FICE settings and the BF, and were blinded to each other's evaluation. The settings used in the study were: FICE 1 (wavelength red 595 nm, green 540 nm, blue 535 nm), FICE 2 (wavelength red 420 nm, green 520 nm, blue 530 nm), FICE 3 (wavelength red 595 nm, green 570 nm, blue 415 nm) and BF (wavelength 490-430 nm). The sequence used by the reviewers was uniform, starting with FICE 1, then FICE 2, FICE 3 and finally the BF.

Variables and outcomes

SBCE-WL and virtual chromoendoscopy images were compared regarding the contrast of mucosal surface and clear demarcation of the borders of the lesions. Each investigator rated the delineation of lesions with each setting of FICE and BF mode as follows: +2 (remarkably better delineation with enhanced delineation of lesion surface and/or borders), +1 (slight improvement), 0 (equivalent to conventional SBCE-WL), -1 (worse delineation or inability to characterize a specific lesion). Finally, the scores attributed by the investigators were added for each lesion, such that a final score $\geqslant 2$ was classified as better delineation, a score between 0 and 1 was considered equivalent to conventional SBCE-WL, and a score $\leqslant -1$ indicated worse delineation with virtual chromoendoscopy.

Statistical analysis

Inter-observer percentage of agreement was determined

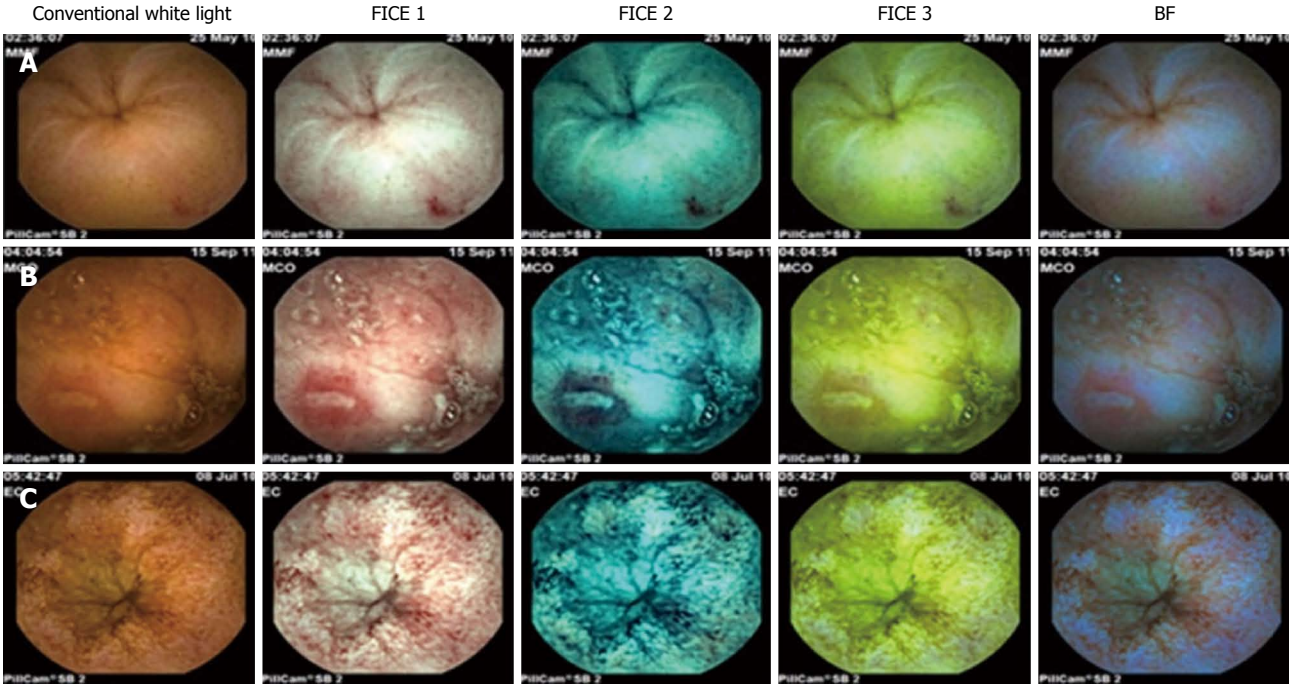

Figure 1 Small bowel mucosal lesions under conventional white light and virtual chromoendoscopy. A: Angioectasia; B: Ulcer; C: Villous edema.

Table 1 Summary of results

	Angioectasias (*n* = 39)	Ulcers/erosions (*n* = 49)	Villous edema/atrophy (*n* = 12)	Overall (*n* = 100)
FICE 1				
Improved delineation	38/39 (97.4%)	31/49 (63.3%)	8/12 (66.7%)	77/100 (77.0%)
Percentage of agreement, κ	97.4%, κ = 0.910	81.6%, κ = 0.714	91.7%, κ = 0.815	89.0%, κ = 0.833
FICE 2				
Improved delineation	38/39 (97.4%)	28/49 (57.1%)	8/12 (66.7%)	74/100 (74.0%)
Percentage of agreement, κ	89.7%, κ = 0.802	79.6%, κ = 0.703	91.7%, κ = 0.815	85.0%, κ = 0.764
FICE 3				
Improved delineation	18/39 (46.2%)	12/49 (24.5%)	0/12 (0.0%)	41/100 (41.0%)
Percentage of agreement, κ	53.8%, κ = NA	75.5%, κ = NA	66.7%, κ = 0.304	66.0%, κ = 0.486
BF				
Improved delineation	6/39 (15.4%)	30/49 (61.2%)	3/12 (25.0%)	39/100 (39.0%)
Percentage of agreement, κ	76.9%, κ = 0.558	81.6%, κ = 0.570	25.0%, κ = NA	79.0%, κ = 0.593

FICE: Flexible Spectral Imaging Color Enhancement; BF: Blue Filter; NA: Not available.

and analyzed using Fleiss *Kappa* coefficient, such that κ *(k)* < 0 indicated poor agreement, 0.00-0.20 slight agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement, and 0.81-1.00 almost perfect agreement[21].

RESULTS

Overall, the delineation of small bowel mucosal lesions was improved in 77% of cases with FICE 1, 74% with FICE 2, 41% with FICE 3 and 39% with the BF, with a percentage of agreement between the two investigators of 89% [κ = 0.833 (*P* < 0.001), 95%CI: 0.741-0.925], 85% [κ = 0.764 (*P* < 0.001), 95%CI: 0.654-0.874], 66% [κ = 0.486 (*P* < 0.001), 95%CI: 0.345-0.627] and 79% [κ = 0.593 (*P* < 0.001), 95%CI: 0.438-0.748], respectively (Table 1). FICE 1 improved the delineation of 97.4% of vascular lesions (angioectasias), 63.3% of mucosal breaks (ulcers/erosions) and 66.7% of villous morphology changes (edema/atrophy), with a percentage of agreement of 97.4% [κ = 0.910 (*P* < 0.001), 95%CI: 0.736-1.084], 81.6% [κ = 0.714 (*P* < 0.001), 95%CI: 0.543-0.885 and 91.7% [κ = 0.815 (*P* < 0.001), 95%CI: 0.470-1.160], respectively. FICE 2 improved the delineation of 97.4% of angioectasias, 57.1% of ulcers/erosions and 66.7% of villous edema/atrophy, with a percentage of agreement of 89.7% [κ = 0.802 (*P* < 0.001), 95%CI: 0.620-0.984], 79.6% [κ = 0.703 (*P* < 0.001), 95%CI: 0.540-0.866] and 91.7% [κ = 0.815 (*P* < 0.001), 95%CI: 0.470-1.160], respectively. FICE 3 improved the delineation of 46.2% of angioectasias, 24.5% of ulcers/erosions and none of the cases of villous edema/atrophy, with a percentage of agreement of 53.8% (κ = NA), 75.5% (κ = NA) and 66.7% [κ = 0.304 (*P* = 0.098), 95%CI: -0.091-0.700],

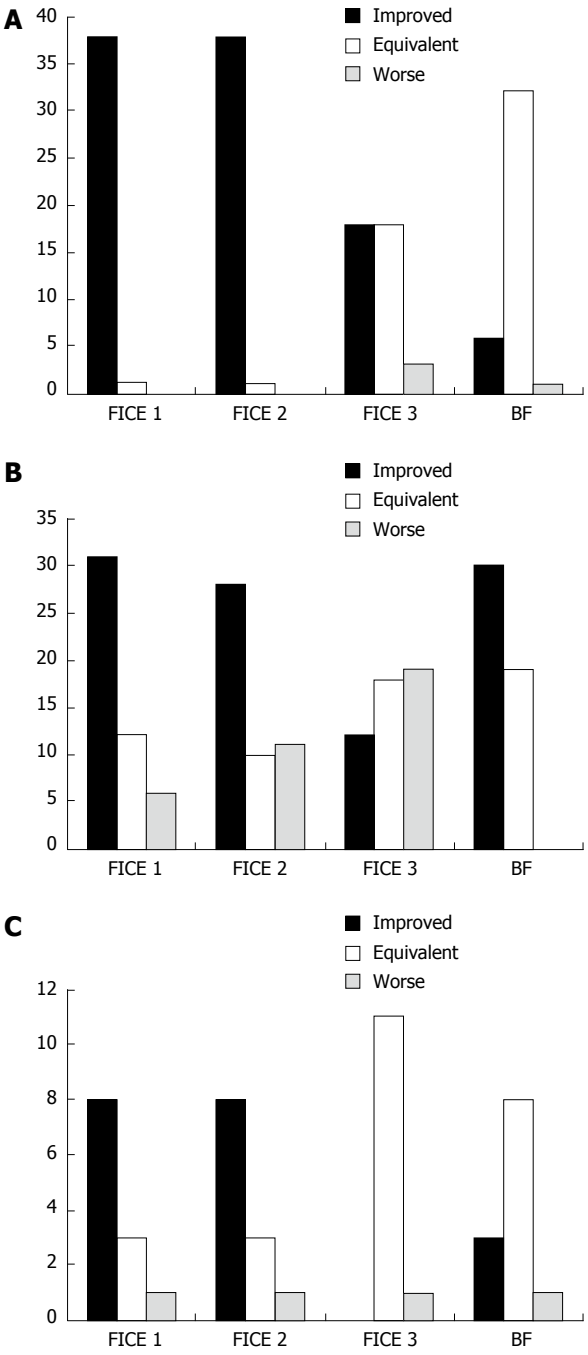

Figure 2 Delineation. A: Of angioectasias with all different settings of virtual chromoendoscopy: comparison with conventional white light; B: Of ulcers or erosions with all different settings of virtual chromoendoscopy: comparison with conventional white light; C: Of villous edema or atrophy with all different settings of virtual chromoendoscopy: comparison with conventional white ligh.

respectively. The BF improved the delineation of 15.4% of angioectasias, 61.2% of ulcers/erosions and 25% of villous edema/atrophy, with a percentage of agreement of 76.9% [κ = 0.558 (P < 0.001), 95%CI: 0.264-0.852], 81.6% [κ = 0.570 (P < 0.001), 95%CI: 0.333-0.807] and 25.0% (κ = NA), respectively. The detailed outcomes in terms of quality of delineation per type of lesion with each setting of virtual chromoendoscopy are summarized in graphical representation for angioectasias (Figure 2A), ulcers/erosions (Figure 2B) and villous edema/atrophy (Figure 2C).

DISCUSSION

Currently available data on the use of virtual chromoendoscopy on SBCE are scarce, with conflicting results reported in the literature regarding its accuracy and clinical value[7,11,22-24]. Moreover, there is ongoing discussion on what should be the optimal settings to improve the detection and/or delineation of different types of lesions[7,19]. Some important questions have been addressed[11], such as whether virtual chromoendoscopy may improve the detection rate of clinically relevant lesions, and whether it may contribute to a better characterization of lesions detected with conventional SBCE-WL. We should underline that a significant number of non-pathological or clinically irrelevant lesions may be detected when FICE is used, such as small red spots or prominent folds that may be erroneously interpreted as angioectasias when FICE is used[22]. Our study did not address this issue, since we did not perform a comparative evaluation of the full video using white light *vs* virtual chromoendoscopy; indeed, all images of the lesions selected to enter the study had been previously identified with SBCE-WL, as we aimed to evaluate whether virtual chromoendoscopy could improve the delineation of the most common lesions in the small bowel detected by the capsule.

We observed that, overall, FICE 1 and FICE 2 improved the delineation of small bowel lesions in up to 77% and 74% of the cases, respectively, with almost perfect interobserver agreement for FICE 1 [κ = 0.833 (P < 0.001), 95%CI: 0.741-0.925] and substantial interobserver agreement for FICE 2 [κ = 0.764 (P < 0.001), 95%CI: 0.654-0.874]. Conversely, the interobserver agreement was moderate with FICE 3 [κ = 0.486 (P < 0.001), 95%CI: 0.345-0.627)] and BF [κ = 0.593 (P < 0.001), 95%CI: 0.438-0.748], and these settings only improved the delineation of lesions in 41% and 39%, respectively. FICE 1 and FICE 2 were particularly useful improving the delineation of angioectasias (97.4% with both settings) and, to a lesser degree, ulcers/erosions (63.3% and 57.1%, respectively) and villous edema/atrophy (66.7% with both settings). Overall, FICE 1 and FICE 2 were superior to FICE 3 and BF for all types of lesions, which is in line with other published data[6,7,25] (Table 2). Interestingly, in the case of ulcers/erosions, the BF yielded good results, comparable to FICE 1 and FICE 2, improving the delineation of 61.2% of lesions, although with a lower interobserver agreement [κ = 0.570 (P < 0.001), 95%CI: 0.333-0.807].

The outcomes per type of lesion may be summarized as follows: the delineation of angioectasias was improved with either FICE 1 or FICE 2 in almost all cases (97.4%); the delineation of ulcers/erosions was improved in 57%-63% of the cases with either FICE 1 (63.3%), FICE 2 (57.1%) or BF (61.2%); the delineation of villous edema/atrophy was improved with either FICE 1 or FICE 2 in approximately two thirds (66.7%) of the cases. As in other published studies[7,19,23], we found FICE 3 to

Table 2 Summary of publications on small bowel capsule endoscopy-virtual chromoendoscopy

Ref.	Center	Study type	No. of patients	Outcome	Results
Imagawa *et al*[7]	Single center	Retrospective	122 patients	Delineation	145 lesions FICE 1: improved delineation in 87.0% (20/23) of angioectasias, 53.3% (26/47) of ulcers/erosions and 25.3% (19/75) of tumors FICE 2: improved delineation in 87.0% (20/23) of angioectasias, 25.5% (12/47) of ulcers/erosions and 20.0% (15/75) of tumors FICE 3: no improvement
Imagawa *et al*[6]	Single center	Prospective	50 patients	Detection rate	FICE 1: increased detection rate of angioectasias (48 *vs* 17, $P = 0.0003$) FICE 2: increased detection rate of angioectasias (45 *vs* 17, $P < 0.0001$) FICE 3: increased detection rate of angioectasias (24 *vs* 17, P = ns) Detection of ulcers, erosions and tumors did not differ significantly between conventional SBCE-WL and SBCE-FICE
Gupta *et al*[22]	Single center	Retrospective	60 patients	Detection rate	157 lesions detected with SBCE-FICE *vs* 114 with SBCE-WL ($P = 0.15$) 5/55 angioectasias were better characterized with SBCE-FICE More P0 diagnosed with SBCE-FICE (39 *vs* 8, $P < 0.001$) Intra-class κ correlations with SBCE-FICE: 0.88 (P2 lesions); 0.61 (P1 lesions) Intra-class κ correlations with SBCE-WL: 0.92 (P2 lesions); 0.79 (P1 lesions) For P2 lesions, the sensitivity was 94% *vs* 97% and specificity was 95% *vs* 96% for SBCE-FICE and SBCE-WL, respectively
Krystallis *et al*[19]	Single center	Retrospective	200 patients	Delineation	167 lesions including angioectasias ($n = 18$), erosions/ulcers ($n = 60$), villi oedema ($n = 17$), cobblestone ($n = 11$), blood lumen ($n = 15$), lesions of unknown clinical significance ($n = 46$) FICE 1: improved delineation in 34%; κ = 0.646 FICE 2: improved delineation in 8.6%; κ = 0.617 FICE 3: improved delineation in 7.7%; κ = 0.669 Blue mode: improved delineation in 83%; κ = 0.786
Duque *et al*[8]	Single center	Prospective	20 patients	Detection rate	150 lesions SBCE-FICE: increased detection rate (95 *vs* 75), κ = 0.650 SBCE-FICE did not miss any lesion identified by CE-WL and allowed the identification of a higher number of angioectasias (35 *vs* 32, $P = 0.25$) and erosions (41 *vs* 24, $P < 0.001$)
Nakamura *et al*[25]	Single center	Prospective	50 patients	Detection rate (QuickView)	SBCE-WL: sensitivity 80%, specificity 100% SBCE-FICE: sensitivity 91% specificity 86% SBCE-FICE resulted in more false positive findings and lower specificity
Sakai *et al*[26]	Single center	Prospective	12 patients	Detection rate	142 lesions including angioectasias ($n = 60$) and ulcers/erosions ($n = 82$) Angioectasias were detected with CE-WL (26/60), SBCE-FICE 1 (40/60), SBCE-FICE 2 (38/60), SBCE-FICE 3 (31/60) Ulcers/erosions were detected with SBCE-WL (38/82), SBCE-FICE 1 (62/82), SBCE-FICE 2 (60/82), SBCE-FICE 3 (20/82) SBCE-FICE 1and 2 significantly increased the detection rate of angioectasias ($P = 0.0017$ and $P = 0.014$, respectively) and ulcers/erosions ($P = 0.0012$ and $P = 0.0094$, respectively) In poor bowel visibility conditions, SBCE-FICE yielded a high rate of false-positive findings
Cotter *et al*	Single center	Retrospective	49 patients	Delineation	100 lesions including angioectasias ($n = 39$), ulcers/erosions ($n = 49$), villous edema/atrophy ($n = 12$) FICE 1: image improvement in 77% (κ = 0.833) FICE 2: image improvement in 74% (κ = 0.764) FICE 3: image improvement in 66% (κ = 0.486) BF: image improvement in 79% (κ = 0.593) FICE 1 improved the delineation of 97.4% of angioectasias, 63.3% of ulcers/erosions and 66.7% of villous edema/atrophy FICE 2 improved the delineation of 97.4% of angioectasias, 57.1% of ulcers/erosions and 66.7% of villous edema/atrophy FICE 3 improved the delineation of 46.2% of angioectasias, 24.5% of ulcers/erosions and none of the cases of villous edema/atrophy BF improved the delineation of 15.4% of angioectasias, 61.2% of ulcers/erosions and 25.0% of villous edema/atrophy

FICE: Flexible Spectral Imaging Color Enhancement; BF: Blue Filter; SBCE-WL: White light small bowel capsule endoscopy.

be ineffective for the vast majority of small bowel mucosal lesions. The results of our study suggest that FICE 1 (wavelengths red 595 nm, green 540 nm, blue 535 nm) seems to achieve the optimal appearance of vascular and mucosal contrast for small bowel lesions, with the highest interobserver agreement among all settings of FICE, and thus it should generally be the setting of choice when using virtual chromoendoscopy. Imagawa *et al*[7] had reported that both FICE 1 and FICE 2 could improve the delineation of ulcers and erosions, however the detection

rate of such lesions was similar between white light and virtual chromoendoscopy[6]. Similarly to our study, Krystallis *et al*[19] reported a better delineation of ulcers using the BF. Duque *et al*[8] reported an improvement in the diagnosis of erosions using FICE 2, due to the enhancement of its inflammatory halo. Regarding villous edema/atrophy, in our study it was better visualized with FICE 1 and FICE 2, while other authors[19] have found edema to be better visualized with the BF mode.

In summary, our results suggest that virtual chromoendoscopy, and particularly FICE 1, may be used in those cases where the characterization or interpretation of small bowel lesions is not straightforward with conventional SBCE-WL. On the other hand, in our study virtual chromoendoscopy did not lead to reclassification of any of the lesions detected with conventional SBCE-WL, and we did not evaluate whether it could contribute to increase the diagnostic yield of SBCE by identifying new lesions previously undetected with SBCE-WL, as we evaluated pre-selected lesions, which had already been previously diagnosed. Moreover, in the absence of a gold standard, it is not possible to accurately assess the false positives rate of these new techniques. Thus, at this point, although virtual chromoendoscopy has been shown to improve the delineation of small bowel lesions previously diagnosed by conventional SBCE-WL, the impact of this technology on the detection rate, accuracy of diagnosis and improved clinical outcome warrants further investigation. Our data support the current use of virtual chromoendoscopy as a complement to conventional white light SBCE for the evaluation of difficult to interpret endoscopic images.

COMMENTS

Background

One of the recent technical advances of small bowel capsule endoscopy (SBCE) is the possibility to enhance endoscopic imaging with computed virtual chromoendoscopy, using the Flexible Spectral Imaging Color Enhancement (FICE) or the Blue Filter (BF) modes. However, it is currently controversial whether virtual chromoendoscopy may increase the diagnostic yield and diagnostic accuracy of SBCE, and what are the optimal wavelength filters to be used.

Research frontiers

The authors aimed to evaluate whether different settings of FICE or the Blue Filter could improve the delineation of the most frequent small bowel mucosal lesions detected by conventional white light small bowel capsule endoscopy (SBCE-WL), namely the three main types of small bowel mucosal lesions: vascular (angioectasias), mucosal breaks (ulcers and erosions) and villous pattern (edema and atrophy).

Innovations and breakthroughs

Virtual chromoendoscopy improved the delineation of three main types of small bowel mucosal lesions: vascular (angioectasias), mucosal breaks (ulcers and erosions) and villous pattern (edema and atrophy). FICE 1 (wavelengths red 595 nm, green 540 nm, blue 535 nm) seems to achieve the optimal appearance of vascular and mucosal contrast for small bowel lesions, with the highest interobserver agreement among all settings of FICE, and thus it should generally be the setting of choice when using virtual chromoendoscopy.

Applications

The results suggest that virtual chromoendoscopy, and particularly FICE 1, may be used in those cases where the characterization or interpretation of small bowel lesions is not straightforward with conventional SBCE-WL. Authors' support the use of virtual chromoendoscopy as a complement to conventional white light SBCE for the evaluation of difficult to interpret endoscopic images.

Terminology

FICE (Fujinon Corporation®, Saitama, Japan) is a computed virtual chromoendoscopy modality that uses a spectral estimation technology, narrowing the bandwidth of white light that permits an automatic reconstruction of pre-acquired conventional endoscopic images into virtual images with different wavelengths of red, green and blue, in order to enhance vascular contrast and the resolution of surface patterns. BF is a different setting of virtual chromoendoscopy consisting of colour enhancement within a short wavelength range (490-430 nm).

Peer review

In a retrospective study, the authors have evaluated virtual chromoendoscopy SBCE in the delineation of small bowel lesions previously detected by white light SBCE. The virtual chromoendoscopy included 3 types of FICE and a blue filter. This is an interesting report.

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RETROSPECTIVE STUDY

Evaluation of diagnostic cytology *via* endoscopic naso-pancreatic drainage for pancreatic tumor

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Author contributions: Iwata T designed the study and wrote the manuscript; Kitamura K managed the medical record; Iwata T, Kitamura K, Sato Y, Nomoto T, Ikegami A and Yoshida H performed this procedure as endoscopic operators; Yamamiya A and Ishii Y helped with this procedure as 2nd operators; Yoshida H was also involved in editing the manuscript.

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Abstract

AIM: To evaluate the usefulness of cytology of the pancreatic juice obtained *via* the endoscopic naso-pancreatic drainage tube (ENPD-C).

METHODS: ENPD was performed in cases where a diagnosis could not be made other than by using endoscopic retrograde cholangiopancreatography and in cases of pancreatic neoplasms or cystic tumors, including intraductal papillary mucinous neoplasm (IPMN) suspected to have malignant potential. 35 patients (21 males and 14 females) underwent ENPD between January 2007 and June 2013. The pancreatic duct was imaged and the procedure continued in one of ENPD-C or ENPD-C plus brush cytology (ENPD-BC). We checked the cytology result and the final diagnosis.

RESULTS: The mean patient age was 69 years (range, 48-86 years). ENPD-C was performed in 24 cases and ENPD-C plus brush cytology (ENPD-BC) in 11 cases. The ENPD tube was inserted for an average of 3.5 d. The final diagnosis was confirmed on the basis of the resected specimen in 18 cases and of follow-up findings at least 6 mo after ENPD in the 18 inoperable cases. Malignancy was diagnosed in 21 cases and 14 patients were diagnosed as having a benign condition. The ratios of class Ⅴ/Ⅳ:Ⅲ:Ⅱ/Ⅰ findings were 7:7:7 in malignant cases and 0:3:11 in benign cases. The sensitivity and specificity for all patients were 33.3% and 100%, respectively. The cytology-positive rate was 37.5% (6/16) for pancreatic cancer. For IPMN cases, the sensitivity and specificity were 33% and 100%, respectively.

CONCLUSION: Sensitivity may be further increased by adding brush cytology. Although we can diagnosis cancer in cases of a positive result, the accuracy of ENPD-C remains unsatisfactory.

Key words: Endoscopic naso-pancreatic drainage; Pancreatic juice; Cytology; Pancreatic cancer; Intraductal papillary mucinous neoplasm

Core tip: This study was performed to evaluate the usefulness of cytology of the pancreatic juice obtained *via* the endoscopic naso-pancreatic drainage tube (ENPD-C). We retrospectively investigated 35 patients with pancreatic disease. ENPD-C was performed in 24 cases and ENPD-C plus brush cytology (ENPD-BC) in 11 cases. The sensitivity and specificity for all patients were 35% and 100%, respectively. The cytology-positive rate was 37.5% (6/16) for pancreatic cancer and 33% (1/3) for intraductal papillary mucinous cancer. Sensitivity may be further increased by adding brush cytology. We can diagnosis cancer in cases of a positive result (class Ⅴ/Ⅳ) but the accuracy of ENPD-C remains unsatisfactory.

Iwata T, Kitamura K, Yamamiya A, Ishii Y, Sato Y, Nomoto T, Ikegami A, Yoshida H. Evaluation of diagnostic cytology *via* endoscopic naso-pancreatic drainage for pancreatic tumor. *World J Gastrointest Endosc* 2014; 6(8): 366-372 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i8/366.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i8.366

INTRODUCTION

The early diagnosis of malignant pancreatic disease is very difficult and, as a result, it is usually only discovered at an advanced stage. Patients with malignant pancreatic disease, especially pancreatic ductal adenocarcinoma (PDAC), have a poor prognosis, and therefore we perform a pathological examination in cases where disease is suspected in order to make a diagnosis as early as possible and to select the optimal treatment strategy. Advancements in imaging techniques, such as computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS), have improved the diagnosis rate, but pancreatic tumors are still generally detected too late for effective treatment. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has recently been employed and now plays a key role in the diagnosis of pancreatic cancer. However, if a mass cannot be detected by imaging, it is correspondingly difficult to diagnose an early pancreatic carcinoma in situ by pathological examination.

Some researchers[1,2] reported that pancreatic juice could be obtained repeatedly *via* an endoscopic naso-pancreatic drainage (ENPD) tube and that this was useful for making a definitive diagnosis of small pancreatic tumors. Furthermore, EUS-FNA is not generally used for cystic tumors in Japan because infectious complications, bleeding and dissemination in a patient with a pancreatic cystic tumor have been reported[3-5]. Diagnosis by cytology and brush cytology using an ENPD tube guided by endoscopic retrograde cholangiopancreatography (ERCP) has also been reported, but with variable rates of detection[6-14]. A few reports have also described the cytology findings of pancreatic juice in cases of branched type intraductal papillary mucinous neoplasm (IPMN)[15]. In this retrospective study, we assessed the diagnostic potential of cytology of pancreatic juice obtained *via* ENPD (ENPD-C) and ENPD-C with brush cytology (ENPD-BC) for the diagnosis of pancreatic neoplasms, including IPMN.

MATERIALS AND METHODS

ENPD was performed in cases where a diagnosis could not be made other than by using ERCP and in cases of pancreatic neoplasms or cystic tumors suspected to have malignant potential. Accordingly, 35 patients (21 males and 14 females) at Showa University Hospital underwent ENPD between January 2007 and June 2013. This procedure was performed by 8 experienced endoscopists. The mean patient age was 69 years (range, 48-86 years) (Table 1). ERCP was performed using a duodenoscope (JF260V; Olympus Medical Systems, Tokyo, Japan). In all cases, we were able to insert a cannula (MTW ERCP catheter; MTW Endoscopy, Wesel, Germany) and a guide-wire (VisiGlide™; Olympus Medical Systems, Tokyo, Japan, or Jagwire™; Boston Scientific, Natick, Mass, United States).

Table 1 Characteristics of patients undergoing endoscopic naso-pancreatic drainage tube and endoscopic naso-pancreatic drainage plus brush cytology

Daiagnostic ENPD (n = 35)	
Age (yr)	69 (48-86)
Sex, M/F	21:14
ENPD-BC (n)	11
Frequency of brush in ENPD-BC (range)	1 (1-2)
Frequency of pancreatic juice cytology in ENPD-BC (range)	4 (2-5)
ENPD-C (n)	24
Frequency of ENPD-C (range)	3 (1-5)

Thirty-five patients underwent the cytology of pancreatic juice obtained *via* endoscopic naso-pancreatic drainage tube (ENPD-C) and ENPD-C with brush cytology (ENPD-BC). M/F: Male/female.

The pancreatic duct was imaged and the procedure continued in one of the following ways: (1) ENPD-BC: In cases of stenosis of the main pancreatic duct, we performed brush cytology (10 single strokes) from the distal tip to the proximal end of the stenosis using a cytology brush (RX Cytology Brushes™; Boston Scientific, Natick, Mass, United States). This was performed in 11 cases. Ultimately, we inserted 5Fr ENPD tubes (Nasal Pancreatic Drainage Set; Cook Medical Inc Endoscopy, Winston-Salem, NC, United States) into the main pancreatic duct; and (2) ENPD-C: After imaging the pancreatic duct, we inserted an ENPD tube into the main pancreatic duct without performing brush cytology in 24 cases.

After steps 1 or 2, we collected the pancreatic juice and submitted it for analysis on the same day or on the following day. Pancreatic juice was obtained *via* the ENPD tube that was inserted for an average of 3.5 d (range, 1-5 d) per patient. All pancreatic juice specimens contained sufficient cells for cytological diagnosis. We occasionally performed additional endoscopic sphincterotomy (EST) in cases of bile duct stenosis or a common bile duct stone, and endoscopic papillosphincterotomy (EPST) was performed in cases of a pancreatic stone. Samples were submitted for cytological examination as soon as possible after collection and the examination tubes contained saline and heparin as rapid on-site specimen evaluation was not possible. If sufficient pancreatic juice could not be obtained by gravity drainage, the specimen was instead obtained by suction. We evaluated the following: (1) the accuracy of cytological analysis of pancreatic juice obtained from pancreatic tumors using ENPD-C and ENPD-BC; (2) the rate of malignancy detected by cytological analysis in cases of pancreatic cancer; (3) the difference in the rate at which cancer was

Table 2 Diagnostic, surgical methods and final diagnosis of pancreatic diseases

		No.
Operable	Pancreaticoduodenectomy	10
	Distal pancreatectomy	3
	Total pancreatectomy	1
	Palliative operation or exploratory laparotomy	4
Inoperable		17
Cancerous	Pancreatic cancer	16
	IPMN-CAN	3
	Others	2
Non-cancerous	IPMN-BEN	8
	Chronic pancreatitis	5
	Others	1

In 18 operable cases, the final diagnosis was confirmed on the basis of the resected specimen. In the 17 inoperable cases, it was diagnosed by follow-up findings at least 6 mo after endoscopic naso-pancreatic drainage (ENPD). The diagnosis of pancreatic ductal adenocarcinoma derived from the intraductal papillary mucinous neoplasm (IPMN-CAN) was only confirmed pathologically in consecutive lesions. We defined IPMN without the potential of cancer as IPMN-BEN.

detected between samples collected by ENPD-C and ENPD-BC; (4) the accuracy of cytological analyses of pancreatic juice for IPMN; and (5) the number and type of complications.

The final diagnosis was based on the surgically resected specimen or on imaging findings in inoperable cases. The diagnosis of PDAC derived from the IPMN (IPMN-CAN) was only confirmed pathologically in consecutive lesions because the distinction between IPMN-CAN and PDAC concomitant with the IPMN is sometimes difficult[15]. Total pancreatectomy was performed in 1 case (2.9%), pancreatoduodenectomy (PD) was performed in 10 cases (28.6%), distal pancreatectomy was performed in 3 cases (8.6%), and palliative surgery was performed in 4 cases. The remaining 17 patients did not undergo surgery (Table 2). The cases diagnosed as being pancreatic cancer included 5 cystic lesions, all of which were classified as IPMN without the potential of cancer (IPMN-BEN). Specimens were categorized using Papanicolaou classification: class Ⅰ, absence of atypical or abnormal cells; class Ⅱ, atypical cytology but no evidence of malignancy; class Ⅲ, cytology suggestive of, but not conclusive for malignancy; class Ⅳ, cytology strongly suggestive of malignancy; and class Ⅴ, cytology conclusive for malignancy. Eight pathologists and 7 cytologists reviewed the cytological examinations of the 35 patients. Cases classified as class Ⅳ/Ⅴ were considered positive, those classified as class Ⅲ were considered borderline-positive, and those classified as class Ⅰ/Ⅱ were considered negative. Class Ⅲ cytology could not be defined as malignant and was therefore considered negative for the determination of sensitivity and specificity. Complications were assessed according to Cotton's classification[16]. Statistical analyses were performed using the Student's t test, χ^2 test or the Fisher exact test, as appropriate. For all tests, $P < 0.05$ was considered significant. All measurements are presented as the median value.

Table 3 Sensitivity and specificity of pancreatic juice cytology

Cytology	Positive	Negative		Total
	Class Ⅴ/Ⅳ	Class Ⅲ	Class Ⅱ/Ⅰ	
Cancerous	7	7	7	21
Non-cancerous	0	3	11	14

The sensitivity and specificity for all patients were 33.3% and 100%, respectively.

RESULTS

The final diagnosis was confirmed on the basis of the resected specimen in 17 cases and on the basis of follow-up findings at least 6 mo after ENPD in the 17 inoperable cases (Table 2). EST was performed in 3 cases and EPST in 4 cases. An ENPD tube was inserted for a median of 3.5 d (range, 1-5 d).

Accuracy of cytological analyses of pancreatic juice obtained by ENPD-C and ENPD-BC in patients with pancreatic tumors

The final diagnosis in 21 cases was of pancreatic malignancy, of which 7 were positive, 7 were false positive, and 7 were negative on ENPD-BC or ENPD-C. The remaining 14 cases found to be benign based on surgical specimens were negative on cytological analysis. Accordingly, the sensitivity and specificity were 33.3% and 100%, respectively, and the accuracy of cytological analysis of pancreatic juice for pancreatic tumors was 60.0%. Although finally diagnosed as benign, cytological analysis of pancreatic juice yielded 3 false-positive results (Table 3).

Rate of malignancy detection by cytological analysis in pancreatic cancer

Sixteen patients were diagnosed as having pancreatic cancer. Cytology results were positive in 6 of these cases, resulting in an accuracy of 37.5%. Five cases of pancreatic cancer were considered to involve a pancreatic cystic lesion. Most pancreatic cancers were located in the pancreatic head (Ph) (12/16, 75.0%), only 1 tumor was located in the body (Pb), and 3 tumors were located in the tail (Pt). The median tumor size was 30 mm (range, 15-54 mm) and the median main pancreatic duct size was 3.5 mm (range, 1-10 mm) (Table 4).

Comparison between the sensitivities of ENPD-C and ENPD-BC

ENPD-BC and ENPD-C was performed in 11 and 24 cases, respectively. In the ENPD-BC group, of the 8 malignant cases, 4 showed positive results (class Ⅴ/Ⅳ) on cytology and 4 showed negative results on cytology [class Ⅲ (3 cases)/Ⅱ/Ⅰ]. In the ENPD-C group, of the 13 malignant cases, 4 showed positive results on cytology (class Ⅴ/Ⅳ) and 9 showed negative results on cytology [class Ⅲ (4 cases)/Ⅱ/Ⅰ]. None of the non-malignant cases showed positive results (class Ⅴ/Ⅳ) on cytology. Thus,

Table 4 Location and size of pancreatic cancer

	Pancreatic cancer
Total	16
Location	
Ph	12
Pb	1
Pt	3
Size (range)	30 mm (15-54 mm)
Main pancreatic duct size (range)	3.5 mm (1-10 mm)

Ph: Head of pancreas; Pb: Body of pancreas; Pt: Tail of pancreas. Most pancreatic cancers were located in the pancreatic head (Ph) (12/16, 75.0%).

the overall sensitivity of ENPD-C and ENPD-BC was 30.8% and 50%, respectively (Table 5).

Accuracy of cytological analysis in patients with IPMN

Three cases of IPMN-CAN were diagnosed on the basis of resected specimens (1 case of branch duct IPMN (BD-IPMN) and 2 cases of main duct IPMN (MD-IPMN)). There were also 8 cases of IPMN-BEN (6 of BD-IPMN and 2 of MD-IPMN). Two IPMN-CANs were located in the Ph and the other was located in the Pt. The median IPMN-CAN size was 43 mm (range, 32-75 mm) and the median IPMN-BEN size was 17.5 mm (range, 10-61 mm), although these differences were not statistically significant (P = 0.081). Mural nodules were observed in all IPMN-CAN cases and in 3 IPMN-BEN cases, but again this difference was not statistically significant (P = 0.182). The diameter of the main pancreatic duct was 6 mm (range, 4-17 mm) in IPMN-CAN cases and 5 mm (range, 3-15 mm) in IPMN-BEN cases (P = 0.530) (Table 6). Cytological examination of pancreatic juice without brush cytology was only performed during ERCP because no stenosis was observed in the main pancreatic duct. One of the 3 IPMN-CAN cases and 2 of the 8 IPMN-BEN cases were classified as class Ⅲ. The sensitivity and specificity of the cytological diagnosis of IPMN was 33% and 100%, respectively, when class Ⅲ cases were considered negative (Table 5).

Complications

The major complication associated with ERCP is post-ERCP pancreatitis[17], although there was only 1 case of post-ERCP pancreatitis in this study (2.9%) in a patient diagnosed as having serous cyst adenoma including non-cancerous cells, located in the Pt. The pancreatitis in this case was relatively mild and resolved after the patient received a nil-by-mouth regimen for a few days. No other complications (such as hemorrhage, cholangitis and perforation) were observed.

DISCUSSION

The number of diagnostic ERCPs has reduced recently with improvements in CT, magnetic resonance imaging and EUS, and the sensitivity, specificity and accuracy of EUS-FNA has been shown to be 85%, 98% and 88%, respectively[5,18], the latter being considerably higher than that of ERCP (18%-70%)[6-8,19-23]. However, it has been reported that cytodiagnosis *via* ENPD can be useful in cases of small pancreatic tumors[1,2]. On occasion, we have not been able to detect small pancreatic tumors due to technical problems, and in these cases, brush cytology and pancreatic juice cytology using ERCP were necessary. However, a number of complications can occasionally arise after ERCP and, according to Vandervoort *et al*[24], its use is followed by pancreatitis in 21% of cases. To date, ERCP for pancreatic cancer diagnosis has been limited to cases in which it is difficult to distinguish between malignant and benign disease by any other modality, complicated by jaundice, cholangitis or an unclear image of the main pancreatic duct by noninvasive examination. When drainage is necessary, it is used for diagnosis and treatment. In our hospital, we perform pancreatic juice cytology and brush cytology using ENPD as necessary, and in the study we report here, there were false-positive cases (class Ⅲ), 7 among the cancer cases and 3 among the non-cancer cases, with an overall sensitivity and specificity of 33.3% and 100%, respectively. In the analysis, false-positive (class Ⅲ) cases were included in the negative group, because these cannot be definitively shown to be malignant. However, if cancer is possible, it might be considered worthwhile to repeat the examination or to perform an operation in order to avoid treatment being given too late. The management of these cases with class Ⅲ findings is a difficult clinical problem. There have been many reports of improved accuracy resulting from changes in the method used to collect pancreatic juice. One of these involved using a catheter or brush cytology and has been reported to result in a sensitivity of 33%-76%[7,9,10] or 30%-84.7%, respectively[11-14]. The sensitivities of ENPD-C and ENPD-BC in these studies were similar at 30.8% and 50%, respectively, but sensitivity may be improved if brush cytology is added to ENPD-C.

The diagnostic utility of ENPD for IPMN is yet to be established as to date, there have only been a few reports on its use[3,25,26]. In the International Consensus Guideline 2012 for the management of IPMN and MCN of the pancreas, routine ERCP for sampling of fluid or brushings in IPMN is not recommended[15]. Hirono *et al*[27] reported that the rate of positive cytology (class Ⅴ/Ⅳ) findings for IPMN-CAN was 11.1%. Another study of a large patient series showed that a carcinoembryonic antigen level greater than 30 ng/mL was a potential diagnostic marker for malignant BD-IPMN. Molecular analysis of cells in pancreatic juice includes an examination of the K-ras codon 12 point mutation, the p53 mutation[28], CD44 expression[29,30] and telomerase activity[30]. Proteomics can also be used to differentiate pancreatic cancer from pancreatitis[31]. However, the diagnostic potential of most of these methods is yet to be established. In our study, using ENPD to diagnose 12 cases of IPMN yielded a sensitivity of 33% and a specificity of 100%. These findings need to be considered with some caution as the study included relatively few cases and was retro-

Table 5 Sensitivity and specificity of endoscopic naso-pancreatic drainage tube with brush cytology and endoscopic naso-pancreatic drainage tube, pancreatic juice cytology and characteristics of intraductal papillary mucinous neoplasm

ENPD-BC (Sensitivity: 50%; Specificity: 100%)	Positive	Negative		Total
11 cases	Class Ⅴ/Ⅳ	Class Ⅲ	Class Ⅱ/Ⅰ	
Cancerous	4	3	1	8
Non-cancerous	0	1	2	3
ENPD-C (Sensitivity: 30.8%; Specificity: 100%)	Positive	Negative		Total
24 cases	Class Ⅴ/Ⅳ	Class Ⅲ	Class Ⅱ/Ⅰ	
Cancerous	4	4	5	13
Non-Cancerous	0	3	8	11
Cytology in IPMN patients (Sensitivity: 33%; Specificity: 100%)	Positive	Negative		Total
	Class Ⅴ/Ⅳ	Class Ⅲ	Class Ⅱ/Ⅰ	
Cancerous	1	1	1	3
Non-cancerous	0	2	6	8

IMPN: Intraductal papillary mucinous neoplasm.

Table 6 Characteristics of intraductal papillary mucinous neoplasm

	IPMN-CAN	IPMN-BEN	*P* value
Total	3	8	
Main duct type	2	2	-
Branch duct type	1	6	
Position			
Ph, Pb, Pt	2, 0, 0	3, 1, 1	-
Pb + Pt	1	1	
Ph + Pt		1	
Ph + Pb + Pt		1	
Size (range)	43 mm (32-75 mm)	17.5 mm (10-61 mm)	0.081[1]
Mural nodule + (%)	3 (100%)	3 (33%)	0.1818[2]
Main pancreatic duct size (range)	6 mm (4-17 mm)	5 mm (3-15 mm)	0.5298[1]

[1]Mann-Whitney *U* test; [2]χ^2 test. None of the differences between the two intraductal papillary mucinous neoplasm (IPMN) groups were significant ($P \geq 0.05$).

spective, but the sensitivity and specificity achieved were similar to those when using pancreatic juice cytology for diagnosing pancreatic tumors and IPMN.

As mentioned above, ERCP is associated with a number of complications, the most common of which is pancreatitis. Cotton *et al*[17] likewise reported that complications (4.0%) were associated with ERCP, including pancreatitis (2.6%) and bleeding (0.3%), identified on follow-up investigations performed over a period of 12 years. In general, post ERCP pancreatitis occurred in 1%-40% of cases and hyperamylasemia was detected in 70% of cases[16]. Vandervoort *et al*[24] reported that pancreatitis occurred in 21% of cases after pancreatic cytology, whilst Ryan *et al*[11] found that it occurred in only 3.2% of cases. These complication rates therefore seem to be study dependent.

Complications for one of the other important modalities for pancreatic solid tumors, EUS-FNA biopsy, occur in only 1%-2% of cases[32]. Pancreatic mass lesions are a suitable indication for EUS-FNA biopsy because of the high diagnostic accuracy and low rate of complications[5]. As the complication rate of ERCP was higher than that of EUS-FNA, it is difficult to argue that ENPD-C and ENPD-BC should be first-line choices. However, they become necessary when a mass cannot be detected by EUS or if the patient has obstructive jaundice or cholangitis requiring drainage. In these cases, we found that ERCP using ENPD for pancreatic diseases including IPMN was an effective alternative. However, additional care is needed when cases are found to be borderline positive, as it is in the case of main pancreatic duct stenosis.

ENPD proved to be a safe technique, but the accuracy with which malignant tumors were detected by cytodiagnosis was low, making further improvements necessary, especially for cases with a border-line positive result. Despite the inclusion of only a small number of cases, the sensitivity and specificity when using pancreatic juice cytology were similar for pancreatic masses and IPMN. Sensitivity may be further increased by adding brush cytology for cases in which there is stenosis of the pancreatic duct. This procedure may not be the first choice of the diagnosis, but we suggest and reconfirm that it is available as one choice of the safe diagnosis method.

COMMENTS

Background

The early diagnosis of malignant pancreatic disease is very difficult. If a small mass cannot be detected by imaging, it is correspondingly difficult to diagnose an early pancreatic carcinoma in situ by pathological examination. Some researchers reported the usefulness of cytology of pancreatic juice obtained repeatedly *via* an endoscopic naso-pancreatic drainage (ENPD) tube.

Research frontiers

The accuracy of the cytology *via* ENPD is uneven in each report. In addition, there are few articles about ENPD for pancreatic neoplasm, including IPMN. Therefore, the authors assessed the diagnostic potential of cytology of pancreatic juice obtained *via* ENPD (ENPD-C) and ENPD-C with brush cytology (ENPD-BC) for the diagnosis of pancreatic neoplasms, including IPMN.

Innovations and breakthroughs

Recent reports have highlighted the importance of more accurate diagnosis for pancreatic tumor before treatment because there is rarely the case of benign disease. The studies suggest that this diagnostic procedure is usable and available if a mass cannot be detected by imaging. Furthermore, this is useful because the sensitivity and specificity in cases of branched type IPMN were similar for pancreatic cancer.

Applications

ENPD proved to be a safe technique, but the accuracy with which malignant

tumors were detected by cytodiagnosis was low, making further improvements necessary, especially for cases with a border-line positive result. Despite the inclusion of only a small number of cases, the sensitivity and specificity when using pancreatic juice cytology were similar for pancreatic masses and IPMN. Sensitivity may be further increased by adding brush cytology for cases in which there is stenosis of the pancreatic duct. This procedure may not be the first choice of the diagnosis, but it is suggested and reconfirmed that it is available as one choice of the safe diagnosis method.

Peer review

This manuscript is about evaluating the usefulness of cytology of the pancreatic juice obtained *via* the ENPD-C. This is an interesting paper that warrants publication.

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PROSPECTIVE STUDY

Endoscopic ultrasound-guided drainage of pelvic abscess: A case series of 8 patients

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Abstract

AIM: To show the safety and effectiveness of endoscopic ultrasound (EUS)-guided drainage of pelvic abscess that were inaccessible for percutaneous drainage.

METHODS: Eight consecutive patients with pelvic abscess that were not amenable to drainage under computed tomography (CT) guidance were referred for EUS-guided drainage. The underlying cause of the abscesses included diverticulitis in 4, postsurgical surgical complications in 2, iatrogenic after enema in 1, and Crohn's disease in 1 patient. Abscesses were all drained under EUS guidance *via* a transrectal or transsigmoidal approach.

RESULTS: EUS-guided placement of one or two 7 *Fr* pigtail stents was technically successful and uneventful in all 8 patients (100%). The abscess was perisigmoidal in 2 and was multilocular in 4 patients. All procedures were performed under conscious sedation and without fluoroscopic monitoring. Fluid samples were successfully retrieved for microbiological studies in all cases and antibiotic policy was adjusted according to culture results in 5 patients. Follow-up CT showed complete recovery and disappearance of abscess. The stents were retrieved by sigmoidoscopy in only two patients and had spontaneously migrated to outside in six patients. All drainage procedures resulted in a favourable clinical outcome. All patients became afebrile within 24 h after drainage and the mean duration of the postprocedure hospital stay was 8 d (range 4-14). Within a median follow up period of 38 mo (range 12-52) no recurrence was reported.

CONCLUSION: We conclude that EUS-guided drainage of pelvic abscesses without fluoroscopic monitoring is a minimally invasive, safe and effective approach that should be considered in selected patients.

Key words: Pelvic abscess; Endoscopic ultrasound -guided drainage

Core tip: For pelvic abscesses that are not amenable to percutaneous drainage, EUS-guided drainage affords a safe and efficient alternative method. The procedure was performed in eight patients under conscious sedation and without a radiological monitoring. One or two plastic stents (7 *Fr*) were placed after dilatation of the tract with a balloon in four patients. Revising this technique by using a cystotome in other four patients appeared feasible and without adverse events. Abscess resolution was documented by imaging examination in all patients. This outcome was not affected although spontaneous stent dislodgment or migration occurred in the majority of patients.

Hadithi M, Bruno MJ. Endoscopic ultrasound-guided drainage of pelvic abscess: A case series of 8 patients. *World J Gastrointest Endosc* 2014; 6(8): 373-378 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i8/373.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i8.373

INTRODUCTION

Infected pelvic fluid collections may occur as a complication of intestinal and gynaecological inflammatory diseases or abdominal surgery.

Unless drainage is promptly achieved, a pelvic abscess is unlikely to heal with conservative measures only, including antibiotics. Historically the treatment of pelvic abscess has been either laparotomy with lavage or blind surgical incision and drainage through the rectal or vaginal wall. Over time management has evolved from operative through percutaneous drainage into endoscopic ultrasound (EUS)-guided transrectal drainage. Case series demonstrate how EUS-guided drainage has passed through various stages of modifications[1-5]. The present case series documents the value of this approach in daily clinical practice and highlights recent developments in this field.

MATERIALS AND METHODS

This is a retrospective analysis of a prospectively collected data of a single centre case series of patients who underwent EUS-guided drainage of pelvic abscess in the period between December 2010 and December 2012. A dedicated pelvic computed tomography (CT) scan was performed before the drainage procedure to determine the exact size and location of the abscess (Figure 1).

EUS-guided drainage was indicated when pelvic abscess was not amenable to drainage by CT guidance due to a lack of adequate and safe window for puncture. At the time of puncture all patients were receiving intravenous antibiotics (amoxicillin plus clavulanic acid or ciprofloxacin) and none had coagulation disorders. Informed consent was obtained from all patients before the procedure. Colon preparation was achieved by administration of polyethyleneglycol (Klean-Prep, Norgine BV, the Netherlands) and natrium phosphate enema (Colex Klysma, Tramedico BV, the Netherlands).

All procedures were performed under conscious sedation by administering a combination of intravenous midazolam and fentanyl. No fluoroscopic monitoring was used during the procedure.

Procedural technique

A therapeutic curvilinear array echoendoscope (EG-160; Olympus®, Tokyo, Japan) with a working channel of 3.2 mm was inserted up to 25 cm from the anal verge. Perirectal and perisigmoidal abscesses (< 15 cm or > 15 cm from anal verge respectively) and the area of contact between the rectal (colonic) wall and abscess wall were located by EUS (Figure 2). Colour doppler was used to exclude the presence of intervening blood vessels in the contact zone.

The abscess cavity was punctured using a 19-A gauge needle (EchoTip; Cook Medical®, Limerick, Ireland) and fluid was aspirated to confirm the location. A sample of aspirated material was sent for microbiological culture. A 0.035-inch guidewire was inserted through the needle and coiled in the cavity under EUS control.

The tract between the rectum and the abscess cavity was created by two different methods. Initially (patients 1-4), a needle knife was inserted into the tract to facilitate the insertion of a biliary balloon (Cook Medical®, Limerick, Ireland). The balloon was then inflated to 8 mm to dilate the tract. In subsequent cases (patients 5-8), the collection was punctured with a 19-gauge FNA needle (Cook Medical®, Limerick, Ireland) through which a guidewire was advanced. After removing the FNA needle, a 10 *Fr* cystotome (Cook Medical®, Limerick, Ireland) was passed over the guidewire under EUS control into the cavity using electro cautery (Figure 3).

The drainage was accomplished by the placement of a 7 *Fr* double pigtail stent across the dilated tract into the abscess cavity (Figure 4). On indication a second stent was inserted after reintroducing the guidewire through a cannula that was passed adjacent to the primary stent under EUS control confirming its adequate positioning in the cavity by fluid/pus aspiration.

Patients continued their antibiotics or were switched according to culture results. Follow-up pelvic CT was performed to assess the response to treatment one week after the procedure. When abscess resolution was verified the stent was endoscopically removed by outpatient sigmoidoscopy. If resolution was not complete (Figure 5) the stent(s) were left in place and pelvic CT was repeated later to confirm abscess resolution prior to stent retrieval.

Technical success was defined as the ability to insert at least one 7 *Fr* pigtail stent to drain the abscess under EUS guidance. Recurrence was defined as the need for repeat EUS-guided drainage of a pelvic abscess after the stent retrieval. Clinical success was defined as complete resolution of the abscess without recurrence or a need for further surgery. The institutional review board of our hospital approved the study.

RESULTS

EUS-guided pelvic abscess drainage was performed in 8 patients (6 men; median age 55.5 years; range 21-74). The clinical features, technical details and outcomes of individual patients who underwent EUS-guided pelvic abscess drainage are shown in Table 1. The abscess was perisigmoidal in 2 and was multilocular in 4 patients. The median size of the abscess was 73 mm (range 45-90) and 43 mm (range 37-55) in the large and small axis respectively.

Stent placement was technically successful in all patients without any adverse events. One patient underwent the procedure twice because during the first attempt the abscess appeared immature without successful fluid aspirate and it was decided not to place a stent. A repeated puncture one week later resulted in evident fluid aspirate and a stent was placed. One stent was placed in six patients and two stents were placed in two patients, one of whom received both transabdominal drain and transrectal stents.

All patients became afebrile within 24 h after drainage

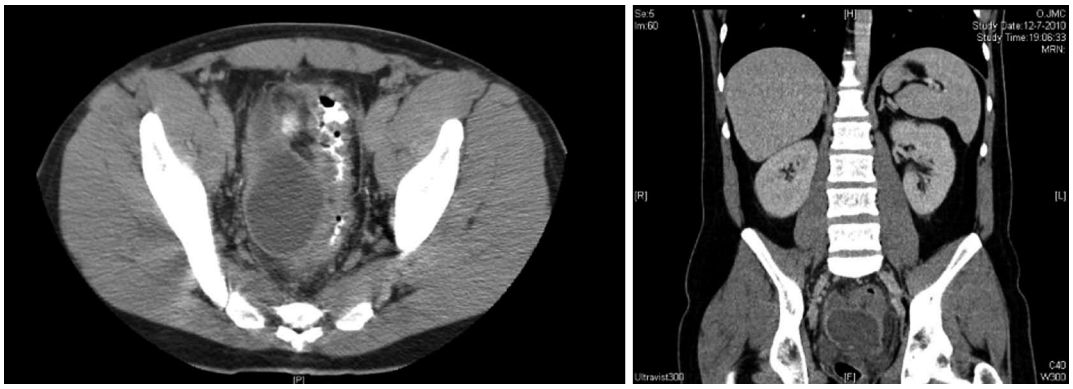

Figure 1 Axial and coronal computed tomography views of pelvic abscess adjacent to thickened sigmoid wall in a patient with acute diverticulitis.

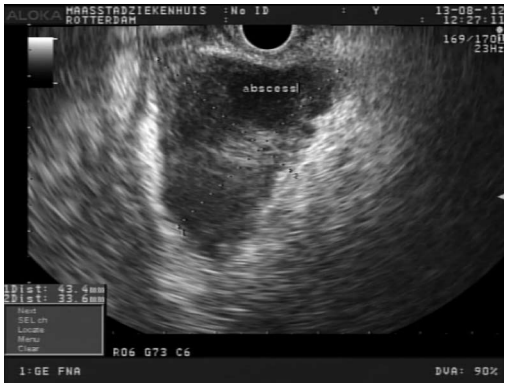

Figure 2 A pelvic abscess (43 mm × 33 mm) visualized with a linear echoendoscope (7.5 MHz).

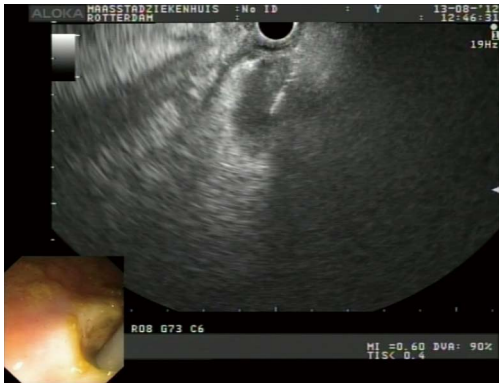

Figure 3 Endoscopic ultrasound (inlet endoscopic) image showing a cystotome used to dilate the tract.

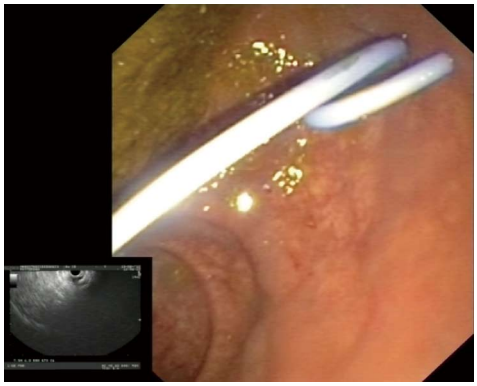

Figure 4 Endoscopic image showing the transrectal placement of 7 *Fr* double pig tail plastic stent.

and the median hospital stay was 8 d (range 4-14). The fluid aspirate microbiological cultures showed a mono- or multibacterial growth of Gram-negative (*Escherichia coli*; *Citrobacter braakii*; *Pseudomonas aeruginosa*) and Gram-positive bacteria (*Haemolytic streptococcus groep F.*; *Enterococcus faecium*; *Staphylococcus aureus*). Antibiotic policy was adjusted according to culture results in 5 patients.

In only two patients the stents were removed during sigmoidoscopy while in the remainder the plastic stent dislocated and spontaneously fell out within one week of its placement. Abscess resolution and spontaneous discharge of the stent was confirmed by means of CT scan one week after the drainage procedure in 6 patients. Stents were endoscopically removed in two patients, respectively 4 and 6 wk after placement at the time when complete resolution of the abscess was confirmed on CT scan.

Within a median follow up period of 38 mo (range 12-52) no recurrence was reported in any patient. Two patients underwent surgery 2 and 3 mo after drainage procedure. One patient had an ileocecal resection for Crohn's disease and another patient a sigmoid resection for recurrent diverticulitis. One patient died 10 mo after the procedure due to metastases from breast cancer.

DISCUSSION

This case series shows that minimally invasive EUS-guided drainage is effective in achieving resolution of pelvic abscesses. Multilocular abscesses also responded favourably to this method indicating internal communications between the different pockets. The procedures were safely performed without fluoroscopy and under conscious sedation. Fluid/pus aspirations for microbiological studies were obtained in all cases to guide antibiotic policy. After EUS guided drainage complete recovery

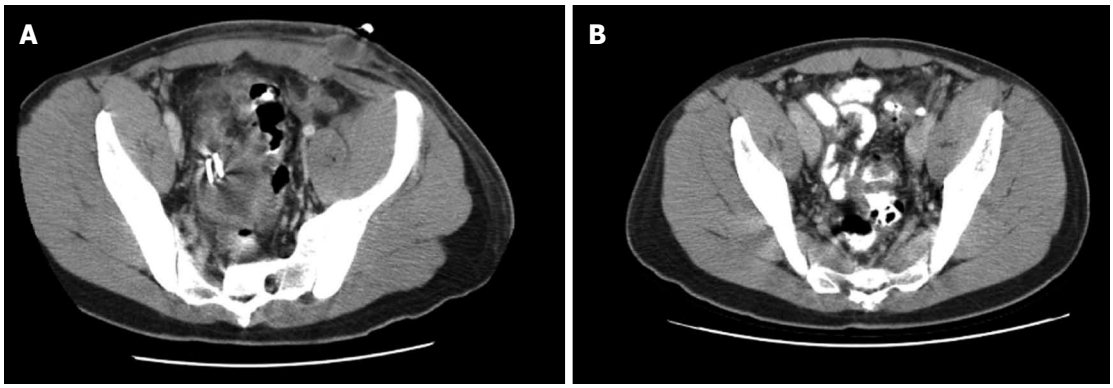

Figure 5 Follow-up computed tomography scans showing initially partial (A) and later complete (B) resolution of pelvic abscess.

Table 1 Clinical details, technical details and outcome of pelvic abscesses treated by endoscopic ultrasound-guided drainage

Patient no.	Abscess location	Etiology	Abscess size (mm)		Abscess type	Cystotome	Stent (s)	Stent spontaneous discharge	Outcome
			Large axis	Small axis					
1	Perirectal	Diverticulitis	90	55	Multilocular	-	2	-	Complete resolution
2	Perirectal	Crohn's disease	45	37	Unilocular	-	1	+	Complete resolution
3	Perisigmoidal	Diverticulitis	75	43	Multilocular	-	2	-	Complete resolution
4	Perirectal	Appendectomy	65	46	Unilocular	-	1	+	Complete resolution
5	Perirectal	Iatrogenic (enema injury)	72	39	Unilocular	+	1	+	Complete resolution
6	Perisigmoidal	Diverticulitis	74	46	Multilocular	+	1	+	Complete resolution
7	Perirectal	Diverticulitis	53	43	Multilocular	+	1	+	Complete resolution
8	Perirectal	Prostate surgery	86	50	Unilocular	+	1	+	Complete resolution

occurred in all patients and in the majority of cases the stent(s) migrated spontaneously. None of the abscesses recurred. In two patients who were operated at a later stage, preoperative abscess drainage under EUS guidance facilitated surgical resection. Application of a cystotome over a guidewire using electrocautery to create a tract proved feasible and safe under endosonographic control.

Pelvic abscess can develop secondary to various intestinal diseases including complicated diverticulitis, appendicitis or Crohn's disease. Gynaecological conditions such as pelvic inflammatory disease and abdominal surgery including low anterior resection for rectal cancer, prostate or obstetrical surgery are also known causes. The most common reported cause is acute diverticulitis causing colonic perforation[6].

When complicated by intra-abdominal rupture, pelvic abscesses can present as a life threatening abdominal emergency with high morbidity and mortality. In addition, conservative treatment alone is seldom effective in achieving complete resolution rendering drainage an unavoidable step in the management of pelvic abscess.

Historically the treatment of pelvic abscess has been either laparotomy with lavage or blind surgical incision and drainage through the rectal or vaginal wall[7]. Later minimally invasive imaging-guided drainage procedures, either computed tomography or ultrasonography, were introduced and established their effectiveness and safety profile[8-11]. However, a small proportion of patients remain inaccessible *via* the transabdominal approach due to lack of an appropriate window for drainage by intervening small bowel loops or blood vessels. In addition, abscess recurrence and/or fistula formation after percutaneous drainage may also complicate the patient's disease course and compromise a surgical approach. Surgical intervention is not infrequent practiced when the abscess is complex and multiloculated, when abscess is inaccessible for minimally invasive drainage, or when a physician experienced in these minimally invasive procedures is not available[11].

The therapeutic application of endoscopic ultrasound (EUS) has gained a wide popularity because of its safety and effectiveness in draining peripancreatic fluid collections *via* the stomach or the duodenum. Accordingly, EUS-guided drainage of deep pelvic abscess could offer an alternative to surgery in selected patients. Since the introduction of this procedure, case series of patients

with pelvic abscesses have reported a high success rate of EUS guided drainage without major complications.

The first report in 2003 described successful EUS-guided stent (8.5-10 *Fr*) placement in 9 of 12 patients and cyst fluid aspiration only in three. Surgical intervention was required in one patient after stent drainage and in two patients in whom the collection was only aspirated. All procedures were performed under general anaesthesia and fluoroscopic monitoring[2]. A subsequent report described the EUS-guided introduction of drainage catheter (10 *Fr*) attached to a flushing system for 4-8 d in four patients with pelvic abscess[3]. In this report, procedures were performed under conscious sedation and fluoroscopic control. Patients with multiloculated abscess were excluded. The same group reported their experience in another 4 patients who successfully underwent the combined placement of one or two double pigtail stents (7 *Fr*) and a single pigtail drainage catheter (10 *Fr*) with favourable outcome[4]. The same centre reported successful placement of either double pigtail stents (n = 15) or double pigtail stents in combination with a single pigtail flushing catheter (n = 10) in patients with deep pelvic abscess < 8 cm or > 8 cm respectively[5]. The flushing drain was removed after 36-72 h and the remaining stents 2 wk after their insertion. Six patients had perisigmoidal abscess. Three patients required a second intervention to replace an inadvertently dislodged drainage catheter and in one patient surgery could not be avoided.

A recent report showed the safety and success of EUS-guided drainage of pelvic abscess without fluoroscopic monitoring in 14 patients[1]. Four patients had pericolonic abscess. Three patients underwent only aspiration after EUS-guided puncture, two patients underwent dilatation with balloon and aspiration, and a single double pigtail stent (10 *Fr*) was placed in nine patients that were removed one week later. All except one recovered completely and one patient needed further surgery within one week after aspiration procedure.

In this series we show that EUS-guided placement of one (or more) 7 *Fr* stent for drainage of pelvic abscesses is safe and has an excellent clinical outcome. Importantly, we did not place any additional flushing catheter and all procedures were completed under conscious sedation without fluoroscopic monitoring. It must be emphasized that the placement of a second stent without fluoroscopic monitoring can be cumbersome or even be associated with adverse consequences and therefore extra caution has to be exercised. The cystotome already has shown its value in the EUS-guided drainage of peripancreatic fluid collections[12,13], and can also be applied to create a tract in case of pelvic abscesses. Despite spontaneous stent migration within one week in 6 out of 8 patients, complete recovery and no relapse occurred in these patients. The spontaneous migration of a stent can be related to the insertion of a relatively small calibre 7 *Fr* pigtail stent in a tract that has been dilated with a balloon or cystotome, the relatively thin muscular layer of rectal (colonic) wall or secondary to peristaltic movements and propulsion of faeces.

It has been argued that transrectal stents can clog easily, particularly because of faecal matter or pus[5]. For this reason, some physicians introduce a nasocystic flushing catheter to continuously irrigate the cavity for some days to enhance resolution of the abscess. According to the results of the present case series as well as others, this step does not seem to be essential to successfully manage pelvic abscesses[1,2]. Although in this series a single 7 *Fr* pigtail stent seemed to suffice in the majority of patients, placement of larger calibre or multiple stents could be helpful to assure adequate drainage in certain individuals.

In conclusion, EUS-guided placement of a single (or more) 7 *Fr* stent for the drainage of pelvic abscesses without fluoroscopic monitoring is safe and has an excellent clinical outcome.

COMMENTS

Background

Deep pelvic abscess can develop as a result of different inflammatory conditions or operations of the distal urogenital or gastrointestinal tract. A proper drainage that is essential for recovery can usually be achieved by percutaneous drainage under radiological monitoring when the abscess is accessible. Endoscopic ultrasound (EUS)-guided transrectal drainage offered alternative drainage route when the latter is not possible.

Research frontiers

The literature addressing this issue is scarce. This study establishes the earlier reported safety and efficacy of this technique in a limited number of case series and widens the total number of patients described to be treated by this method.

Innovations and breakthroughs

The study reports the technical and procedural modifications indicating that a short term drainage with a plastic stent may be sufficiently effective leading to recovery. Furthermore, the study shows for the first time that a cystotome can be employed safely to dilate the drainage tract in this setting without adverse events.

Applications

EUS-guided drianage of deep pelvic abscess not amenable to percutaneous drainage using a cystotome can be safely applied in clinical practice to treat selected cases.

Terminology

Pelvic abscess, endoscopic ultrasound guided drianage.

Peer review

The manuscript describe EUS-guided pelvic abscess drainage in 8 patients. This is a promising technique that has been used recently.

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RANDOMIZED CLINICAL TRIAL

Bowel preparation for colonoscopy using standard *vs* reduced doses of sodium phosphate: A single-blind randomized controlled study

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Abstract

AIM: To evaluate the efficacy of a colonoscopy preparation that utilizes a reduced dose of sodium phosphate (NaP) and an adjunct.

METHODS: Sixty-two patients requiring screening colonoscopies were studied. Each patient was randomly allocated to receive either 50 NaP tablets (50 g) or 30 NaP tablets (30 g) with 10 mL of 0.75% sodium picosulfate for bowel preparation. NaP was administered at a rate of five tablets (5 g) or three tablets (3 g) every 15 min with 200 mL of water, beginning five to six hours before colonoscopy. The sodium picosulfate was administered with 200 mL of water on the night before the procedure. Both groups were compared in term of the efficacies of colonic cleansing, the time required for completion of the bowel preparation, and acceptability of the preparation.

RESULTS: Sixty patients (n = 30 for each group) were analyzed. The cleansing efficacy tended to be higher in the 30 g NaP plus sodium picosulfate group as assessed by the mean total Ottawa scale score (50 g NaP 6.70 ± 1. 42 *vs* 30 g NaP plus sodium picosulfate 6.17 ± 1.18 P = 0.072). The mean time for bowel preparation tended to be shorter in the 30 g NaP plus sodium picosulfate group (50 g NaP 189.9 ± 64.0 min *vs* 30 g NaP plus sodium picosulfate 161.8 ± 57.6 min, P = 0.065). There were no significant differences between the two groups in the acceptability of the preparations (50 g NaP 83.3% *vs* 30 g NaP plus sodium picosulfate 86.7%, P = 0.500). There were no adverse events related to bowel preparation in either of the groups.

CONCLUSION: The colonoscopy preparation that utilized 30 g NaP with sodium picosulfate was comparable to that utilizing 50 g NaP. This novel bowel preparation might be useful before colonoscopy.

Key words: Bowel preparation; Colonoscopy; Colonoscopy preparation; Sodium phosphate; Sodium picosulfate

Core tip: Oral sodium phosphate (NaP) is used for bowel preparation before colonoscopy. It is desirable to reduce the dose of NaP due to the potential adverse events associated with NaP. In this study, we evaluated the efficacy of a colonoscopy preparation that utilized a reduced dose of NaP and an adjunct. This study demonstrated that 30 g NaP in combination with sodium picosulfate can be useful for bowel preparation prior to colonoscopy in Japanese populations. This report is the first to evaluate the efficacy of a bowel preparation using the minimally effective dose of NaP and an adjunct.

Koshitani T, Kawada M, Yoshikawa T. Bowel preparation for colonoscopy using standard *vs* reduced doses of sodium phosphate: A single-blind randomized controlled study. *World J Gastrointest Endosc* 2014; 6(8): 379-384 Available from: URL:

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INTRODUCTION

The quality of bowel preparation influences the diagnostic accuracy of colonoscopy. Inadequate preparation negatively affects rates of polyp[1] and adenoma detection[2] during the procedure. The ideal preparation for colonoscopy would rapidly and reliably eliminate the colon of all fecal material without causing any gross or histological alternations of the colonic mucosa[3,4]. Additionally, the preparation should not cause any patient discomfort and should be safe.

Oral sodium phosphate (NaP), which draws water into the bowel lumen and stimulates peristalsis and evacuation, is used for bowel preparation prior to colonoscopy. Although this agent provides superior cleansing and is well-tolerated by most patients, there are concerns about its safety that are related to its osmotic action[5,6]. Moreover, recent reports[7-9] of renal injury associated with this agent have raised additional concerns. Given the mechanistic causes of the occurrence of adverse events, the use of reduced doses of NaP might decrease these potential risks. We hypothesized that the dose of NaP could be reduced if NaP is combined with an adjuvant colonic laxative for bowel preparation. Sodium picosulfate (SP) is a laxative that stimulates colonic movement and promotes evacuation. SP is often used as an adjunct to polyethylene glycol (PEG) for bowel preparation in Japan. In this study, we present a new method of bowel preparation prior to colonoscopy that utilizes a reduced dose of NaP in combination with SP, and we evaluated the efficacy of this method.

MATERIALS AND METHODS

This study was an investigator-blinded, randomized controlled trial. Outpatients visiting the health check-up center for screening colonoscopies were invited to participate in the study. Due to the potential for NaP preparations to induce fluid shifts and the recent results of the manufacturer's post-marketing trial to assess the incidence of renal injury, patients with the following conditions were excluded: over 65 years of age with hypertension, ascites, renal insufficiency, congestive heart failure, and concurrent use of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). The study was designed in accordance with the Declaration of Helsinki and was approved by the ethics committee of our institute. Written informed consent was obtained from all patients.

Protocol for the study of bowel preparations

All eligible patients were instructed to eat a low-fiber diet on the day before the colonoscopy and to abstain from food after 9 PM on the evening before the procedure. Each patient was randomly allocated to receive either 50 NaP tablets (50 g; Visiclear® ZERIA Pharmaceutical Co., Ltd., Tokyo, Japan) or 30 NaP tablets (30 g) plus 10 mL of 0.75% SP solution (Laxoberon® TEIJIN Pharmaceutical Co., Ltd., Tokyo, Japan) for bowel preparation. The randomization was conducted *via* the use of sealed envelopes with treatment allocations inside and by an investigator who was not involved in the colonoscopy procedure. NaP was administered at a rate of five tablets (5 g) or three tablets (3 g) every 15 min with 200 mL of water beginning five to six hours before the colonoscopy. SP was taken with 200 mL of water on the night before the procedure (Figure 1).

Evaluation of the preparations

The primary end point of this study was cleansing efficacy. The secondary outcomes included time for completion of the bowel preparation and acceptability of the preparation. Upon arriving to the health screening center, the patients submitted a compliance that detailed whether the drugs prescribed for bowel preparation had been taken properly, the time at which the NaP intake was initiated, and when the patients had clear stools. The patients were also asked to complete a written questionnaire to assess their overall impressions of the drugs used for bowel preparation on a 4-category Likert scale and yes or no answers regarding whether they experienced nausea, vomiting, bloating, abdominal pain or other symptoms. The efficacy of the colonic cleansing was graded using the Ottawa Bowel Preparation Scale (OBPS)[10] by a single endoscopist who was blinded to the doses of NaP. This scale uses scores for cleanliness of the recto-sigmoid colon, middle colon, and right colon that range from 0 to 4 (0 = excellent to 4 = inadequate). There is also a score for the overall volume of fluid that ranges from 0 to 2 (0 = small to 2 = large). The overall potential scores range from 0 (excellent preparation, no fluid) to 14 (inadequate in all segments with a large amount of fluid). The time for completion of the bowel preparation was defined as the time from the initiation of NaP until clear stools were noted. The acceptability of the bowel preparation was assessed by the patient's overall impression on a four-category Likert scale: (1) acceptable; (2) relatively acceptable; (3) relatively unacceptable; and (4) unacceptable. Acceptability was defined as the rate of "acceptable" plus "relatively acceptable" responses. The groups were compared for the efficacies of the colonic cleansings, the times for the completion of the bowel preparations, and the acceptabilities of the preparations.

Statistical analysis

In this pilot study, the sample size was arbitrarily set at 30 patients per treatment arm to compare the two bowel preparation regimens. Continuous variables are reported as the mean ± SD, and categorical variables are presented as percentages. For the primary end point, a Mann-

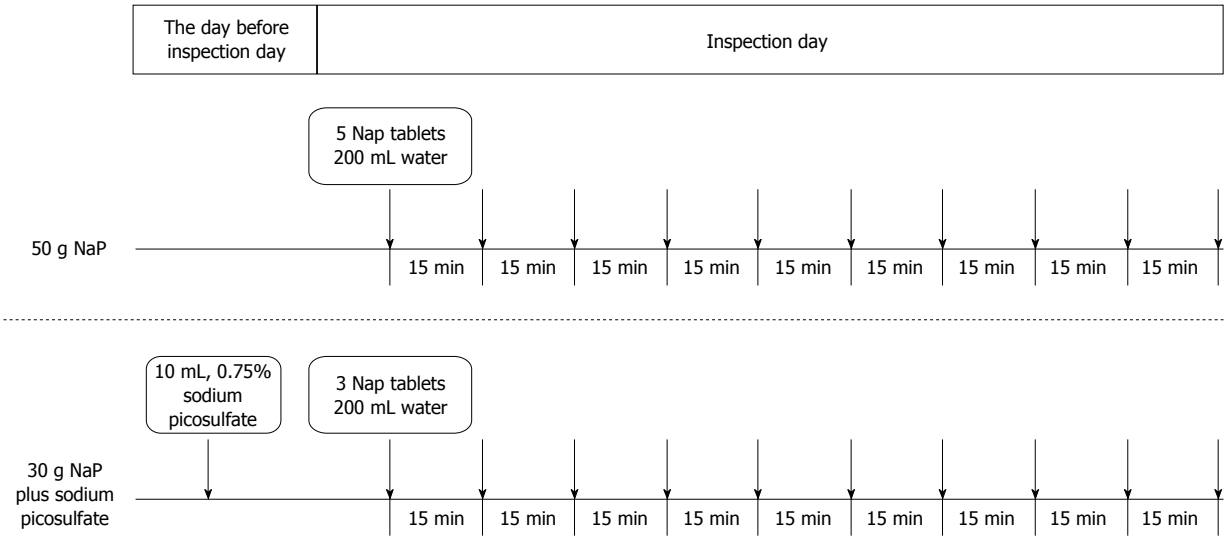

Figure 1 Study protocol for the bowel preparations. Sodium phosphate (NaP) was administered at a rate of five tablets (5 g) or three tablets (3 g) every 15 min with 200 mL of water beginning five to six hours before the colonoscopy. Sodium picosulfate was taken with 200 mL of water on the night before the procedure.

Table 1 Baseline characteristics

	50 g NaP (n = 30)	30 g NaP plus sodium picosulfate (n = 30)	P value
Man/female	23/7	25/5	0.747[1]
Age (yr)	55.4 ± 9.4	55.9 ± 10.8	0.829[2]
Height (m)	1.66 ± 0.08	1.67 ± 0.09	0.575[2]
Weight (kg)	65.7 ± 10.8	66.7 ± 10.0	0.695[2]
BMI (kg/m^2)	23.8 ± 2.6	23.9 ± 2.2	0.929[2]

[1]Student's t-test; [2]Fisher exact test. BMI: Body mass index; NaP: Sodium phosphate.

Whitney U-test was applied to compare the OBPS scores. For the secondary outcomes, Student's t-test was applied to compare the times for the completion of the bowel preparations. The Fisher's exact test was used to compare the acceptabilities of the preparations. Differences with P-values below 0.05 were considered statistically significant.

RESULTS

A total of sixty-two patients were enrolled in the study from July 2012 to September 2013. One patient (30 g NaP plus SP group) was excluded from the study due to inadequate intake of NaP tablets. Another patient (50 g NaP group) completed the preparation but was not assessed for cleansing efficacy due to a previous surgery and was also excluded. Lastly, sixty patients (n = 30 for each group) were included in the analysis. There were no significant differences between the two groups in baseline characteristics, including gender, age, height, weight and body mass index (Table 1).

Efficacy of colonic cleansing

The mean total OBPS score of the 50 g NaP and 30 g NaP plus SP groups were 6.70 ± 1.42 and 6.17 ± 1.18 respectively. There was a trend toward greater cleansing efficacy in the 30 g NaP plus SP group. However, this difference was not statistically significant (P = 0.072). When the mean scores for each component of the OBPS (*i.e.*, the scores for the recto-sigmoid colon, middle colon, right colon, and the volume of fluid) were analyzed, no significant differences between the two groups were found (Figure 2).

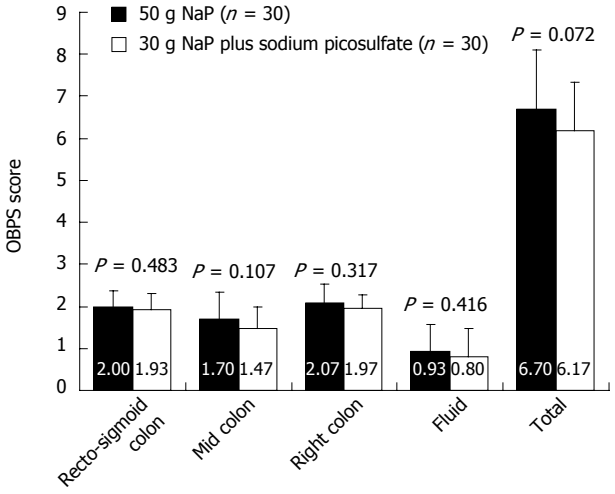

Figure 2 The mean Ottawa bowel preparation scale scores. There was a trend toward a lower mean total score in the 30 g NaP plus sodium picosulfate group compared to the 50 g NaP group, but this difference was not statistically significant (Mann-Whitney's U-test, P = 0.072).

Times for the completion of the bowel preparation

The mean times for the completion of the bowel preparation in the 50 g NaP and 30 g NaP plus SP groups were 189.9 ± 64.0 min and 161.8 ± 57.6 min, respectively. There was a trend toward a shorter bowel preparation

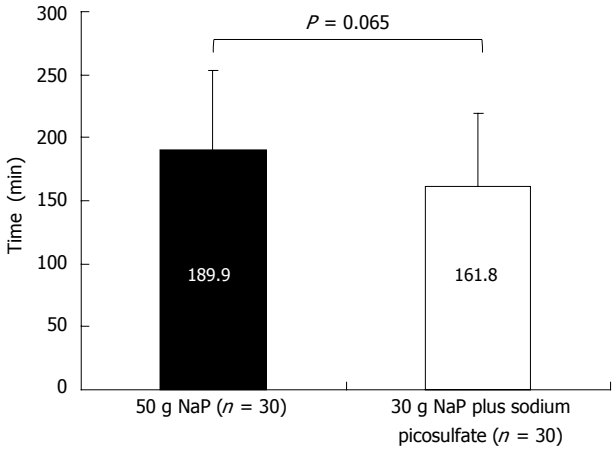

Figure 3 The mean time required for the completion of the bowel preparation. There was a trend toward a shorter bowel preparation time in the 30 g sodium phosphate (NaP) plus sodium picosulfate group compared to the 50 g NaP group, but this difference was not statistically significant (Student's *t*-test, $P = 0.065$).

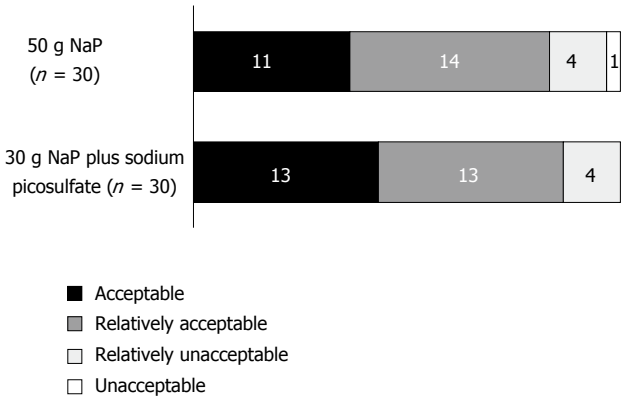

Figure 4 The patients' overall impressions of the bowel preparations as assessed on a four-category Likert scale. There was no significant difference between the two groups in acceptabilities (*i.e.*, the "acceptable" plus "relatively acceptable" scores) of the preparations (Fisher's exact test, $P = 0.500$).

time in the 30 g NaP plus SP group. However, this difference was not statistically significant ($P = 0.065$, Figure 3).

Acceptability of the preparations and adverse events

The patients' overall impressions of the bowel preparations as rated on a four-category Likert scale are shown in Figure 4. The acceptabilities (*i.e.*, the "acceptable" plus the "relatively acceptable" scores) of the preparation in the 50 g NaP and 30 g NaP plus SP groups were 83.3% and 86.7%, respectively. There was no significant difference between the two groups in the acceptabilities of the preparations ($P = 0.500$). The proportions of patients who reported symptoms after taking 50g NaP and 30 g NaP plus SP were 50% and 20%, respectively. There were no adverse events related to the bowel preparations in either of the groups.

DISCUSSION

PEG is an osmotically balanced electrolyte lavage solution that is widely used for bowel preparation prior to colonoscopy. PEG was introduced by Davis *et al*[11] in 1980. PEG passes through the bowel without net absorption or secretion, and significant fluid and electrolyte shifts are therefore avoided. The standard four-liter dosing regimen that is given the day before the procedure has been established as safe and effective[12-14]. However, poor compliance due to the salty taste, sulfate smell, and the large volume of solution required led to modifications of PEG preparation regimens[15,16].

NaP osmotically draws plasma water into the bowel lumen to promote colonic cleansing and is used as an alternative to PEG for bowel preparation prior to colonoscopy[5,6,17]. Oral NaP is available as an aqueous solution and in a tablet form. The tablet form of NaP was designed to improve the taste and limit the volume of liquid required. Phase Ⅲ trials in which tablet NaP regimens were compared with four-liter PEG regimens demonstrated equal colon cleansing with fewer side effects of the NaP regimen[17]. Recent reviews and a meta-analysis have reported that NaP preparations are generally more effective and better tolerated than are PEG formulations[18,19].

The tablet preparation contains 1.5 g NaP and 0.5 g of inactive ingredients. One of the inactive tablet ingredients, microcrystalline cellulose (MCC), is thought to reduce visibility during colonoscopy. Consequently, new MCC-free preparation is now available[20,21]. The doses are 40 tablets (60 g) for the MCC-containing preparation and 32 tablets (48 g) for the MCC-free preparation[22]. Both preparations are divided into two doses that are administered at an interval of 10 to 12 h. All NaP regimens should be taken with a minimum of two liters of clear liquids. In Japan, a MCC-free tablet preparation that contains 1.0 g NaP is commercially available. The standard dose is 50 tablets (50 g), which are taken as five tablets every 15 min with 200 mL of water or green tea on the day of the procedure.

Because of its osmotic mechanism of action, NaP can result in potentially fatal fluid and electrolyte shifts, particularly in elderly patients and patients with bowel obstructions, small intestine disorders, renal or liver insufficiency, or congestive heart failure[23]. Additionally, a recent series of reports[7-9] described acute phosphate nephropathy followed by chronic renal insufficiency after taking NaP for bowel preparation. Nephrocalcinosis is the cause of renal injury and occurs when the concentration of phosphate increases, and calcium phosphate crystals are deposited in the renal tubules[9]. In a series of 21 patients who developed acute phosphate nephropathy, potential etiological factors included dehydration, increased age, hypertension, and concurrent use of an ACE inhibitor or ARB[8]. We conducted our study to examine the use of a preparation that involved a reduced dose of NaP because such a reduction might decrease the potential for adverse events.

Bowel preparations are typically judged by their efficacy, tolerability, and safety, and all three criteria have

obvious clinical importance. The preparation time needed to cleanse the colon of fecal material is also an important factor for bowel preparations. In this pilot study, 30 g NaP plus SP tended to produce higher cleansing efficacy and a shorter bowel preparation time than did the 50 g NaP; however, these differences were not statistically significant. Additionally, this new bowel preparation method was acceptable to more than 85% of patients. These results indicate that the dose of NaP can be reduced to 30 g when it is combined with SP for bowel preparation.

In conclusion, although our study is a trial with a small number of cases from a single center, this report is the first to evaluate the efficacy of a bowel preparation that involves the minimally effective dose of NaP and an adjunct. This study demonstrated that 30 g NaP in combination with SP can be useful for bowel preparation prior to colonoscopy in Japanese populations.

COMMENTS

Background

Sodium phosphate (NaP) is a superior colonic cleanser and is well-tolerated; however, there are concerns about the potential to cause adverse events that include electrolyte shifts and renal injury.

Research frontiers

It is desirable to reduce the dose of NaP required for colonoscopy preparation.

Innovations and breakthroughs

In this study, a new method of colonoscopy preparation that utilizes a reduced dose of NaP and an adjunct was evaluated.

Applications

This study demonstrated that 30 g NaP in combination with sodium picosulfate (SP) can be useful for bowel preparation prior to colonoscopy.

Terminology

SP is often used as an adjunct to polyethylene glycol for bowel preparation in Japan.

Peer review

This is an interesting research article about a common clinical problem related to bowel cleaning prior to colonoscopy examinations. The study was well designed, and its results were clearly demonstrated.

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CASE REPORT

Lymphoepithelioma-like esophageal carcinoma with macroscopic reduction

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Masaya Uesato, Tuguaki Kono, Tooru Shiratori, Yasunori Akutsu, Isamu Hoshino, Kentarou Murakami, Daisuke Horibe, Tetsurou Maruyama, Yoshihide Semba, Ryuma Urahama, Yukiko Ogura, Hisahiro Matsubara, Department of Frontier Surgery, Chiba University Graduate School of Medicine, Chiba 260-8677, Japan

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Abstract

Esophageal lymphoepithelioma-like carcinoma (LELC) is extremely rare. We report the first case of esophageal LELC showing macroscopic reduction. A 67-year-old male presented with dysphagia and, by endoscopic examination, was found to have a significantly raised tumor of 10 mm in diameter in the thoracic esophagus. The biopsied material showed esophageal cancer. We performed endoscopic submucosal dissection. However, the tumor became flattened, similar to a scar, in only 2 mo. Histologically, the carcinoma cells had infiltrated the submucosal layer. Prominent infiltration of T lymphoid cells that stained positive for CD8 was observed around the carcinoma cells. Therefore, this lesion was considered to be an LELC with poorly differentiated squamous cells. Because the margin was positive, an esophagectomy was performed. Carcinoma cells were detected in the neck in one lymph node. The staging was T1N0M1b. However, the patient has been well, without adjuvant therapy or recurrence, for more than 5 years.

Key words: Esophageal cancer; Lymphoepithelioma-like carcinoma; Lymphoid stroma; Tumor-infiltrating lymphocyte; Cytotoxic T lymphocyte; Reduction

Core tip: The first case of esophageal lymphoepithelioma-like carcinoma showing macroscopic reduction is reported. In only 2 mo, the appearance of the esophageal tumor changed from a protruding lesion to a flat scar-like entity. After esophagectomy, one lymph node was diagnosed with metastasis. Prominent infiltration of T lymphoid cells that stained positive for CD8 was observed around the carcinoma cells. Strong expression of human leukocyte antigen-DR was evident in the cell membrane. The immune responses against the main tumor and the denatured carcinoma cells in the metastatic lymph node developed at the same time. Therefore, systemic immune responses against the carcinoma might have been occurring.

Uesato M, Kono T, Shiratori T, Akutsu Y, Hoshino I, Murakami K, Horibe D, Maruyama T, Semba Y, Urahama R, Ogura Y, Oide T, Tanizawa T, Matsubara H. Lymphoepithelioma-like esophageal carcinoma with macroscopic reduction. *World J Gastrointest Endosc* 2014; 6(8): 385-389 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i8/385.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i8.385

INTRODUCTION

Lymphoepithelioma-like carcinoma (LELC) is defined as a tumor with histological similarity to undifferentiated nasopharyngeal carcinoma, with lymphoid stroma (lymphoepithelioma) that occurs outside the nasopharynx. Although LELC has been detected in the salivary gland[1], stomach[2], thymic gland[3], breast[4], and lungs[5], it is extremely rare in the esophagus[6]. The prognosis of patients suffering from this type of cancer has been reported to be favorable[7]. However, there have been no reports of a tumor being reduced macroscopically.

We herein describe the treatment of a patient suffering from an esophageal LELC that spontaneously became small macroscopically and also discuss the results of a pathological analysis of the tumor.

CASE REPORT

A 67-year-old Japanese male with a seven-month history of intermittent dysphagia underwent an upper endoscopic examination at another clinic in May 2008 (Figure 1A) and was diagnosed as having squamous cell carcinoma of the esophagus, with prominent infiltration of lymphoid cells, based on biopsied material (Figure 2). He was admitted to our hospital for treatment in June 2008. No familial disease and no history of previous gastrointestinal disorders were documented. The patient was a heavy drinker and a non-smoker. A physical examination and laboratory data on admission did not reveal any abnormalities.

A barium esophagogram demonstrated a protruding lesion of 10 mm in diameter on the left and posterior wall of the middle thoracic esophagus. An endoscopic examination in June 2008 revealed a raised tumor with a central dip 33 cm from the upper incisors (Figure 1B). Moreover, the tumor had a smooth surface, similar to a submucosal tumor. Endoscopic ultrasonography in July 2008 demonstrated a well-circumscribed, hypoechoic mass originating in the mucosa, without involvement of the submucosal layer. A computed tomography (CT) scan revealed no metastasis. Therefore, we believed that endoscopic submucosal dissection of the tumor was possible and performed the procedure in July 2008.

However, the tumor became flattened, similar to a scar (Figure 1C), and there was a superficial smooth tumor measuring 6 mm × 3 mm in the resected mucosa (Figure 3A). Histologically, the large-sized carcinoma cells formed small focal nests and infiltrated into the submucosal layer, 400 μm from the muscularis mucosae (Figure 3B). Prominent infiltration of T lymphoid cells, which stained positive for CD8, was observed between and around the carcinoma cells (Figure 4A and B). Based on these histopathological features, this lesion was considered to be an LELC with poorly differentiated squamous cells. The other pathological findings included human leukocyte antigen-DR (HLA-DR), strongly positive (Figure 4C); p53, strongly positive; Ki67, moderately positive; and Epstein-Barr virus (EBV)-encoded small RNA1 (EBER-1), negative. Because the vertical margin was positive, a subtotal esophagectomy and dissection of the lymph nodes were performed in October 2008. No remnant tumor was found. However, carcinoma cells were detected in the neck area in one of the 53 dissected lymph nodes (Figure 5).

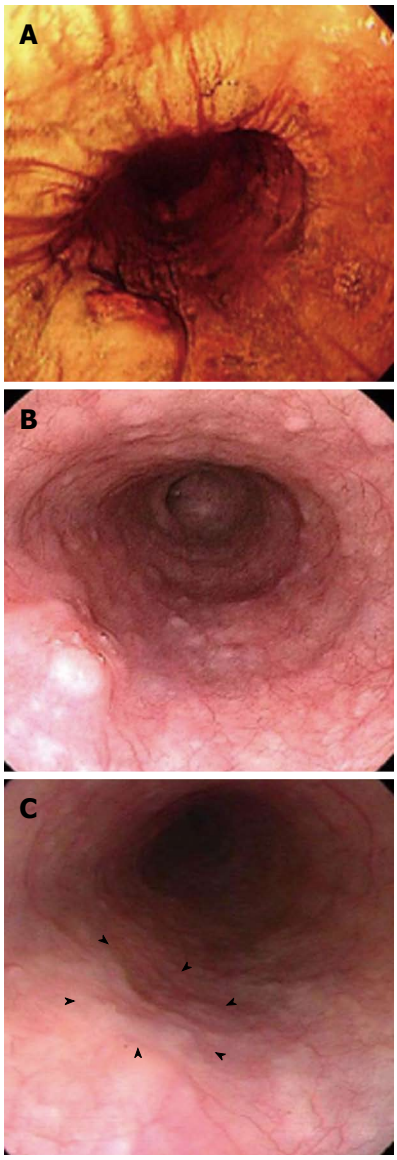

Figure 1 The endoscopic findings. A: The first endoscopy (at the previous clinic) showed a submucosal-like tumor of approximately 10 mm in diameter. The lesion, except for the erosion at the top, was stained with Lugol's solution; B: The second endoscopy (performed two weeks after the first endoscopy) showed a raised tumor with a central dip. The height of the tumor had decreased; C: The third endoscopy (performed during the endoscopic operation, two months after the first endoscopy) showed that the tumor had become flattened, similar to a scar (arrowhead).

According to the tumor node metastasis (TNM) classification of esophageal cancer, the tumor was diagnosed to be stage IVB (T1, N0, M1b). However, many denatured carcinoma cells were observed in the metastatic lymph node (Figure 5B). The patient's postoperative course was uneventful, and he was discharged two weeks

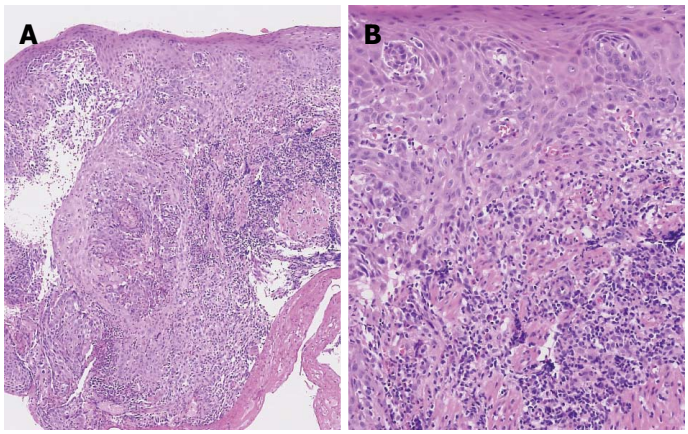

Figure 2 The endoscopically-biopsied material. A: The inflammatory cell infiltration in the mucosa was remarkable (HE staining, original magnification × 40); B: Squamous cell carcinoma with prominent infiltration of lymphoid cells was revealed (HE staining, original magnification × 100).

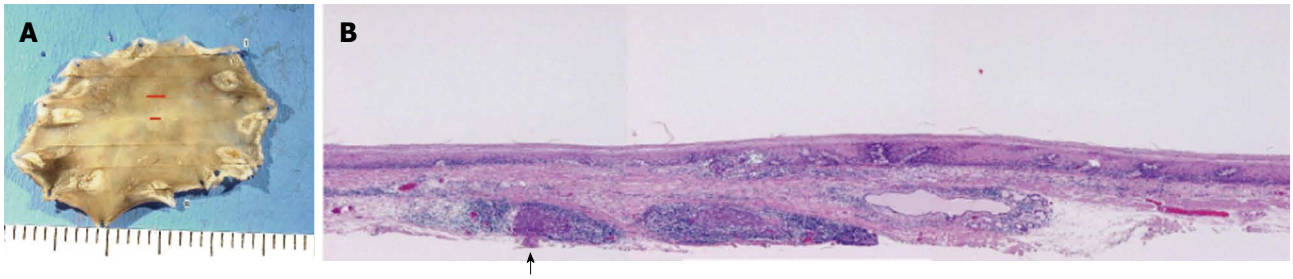

Figure 3 The endoscopically-resected material. A: The gross appearance of the resected esophageal mucosa is shown. There was a superficial smooth tumor measuring 6 mm × 3 mm in the resected mucosa (line), and it was difficult to find the tumor macroscopically; B: The tumor, with prominent lymphoid cell infiltration, was mainly visible in the submucosal layer (HE staining, original magnification × 10). The vertical margin was positive (arrow).

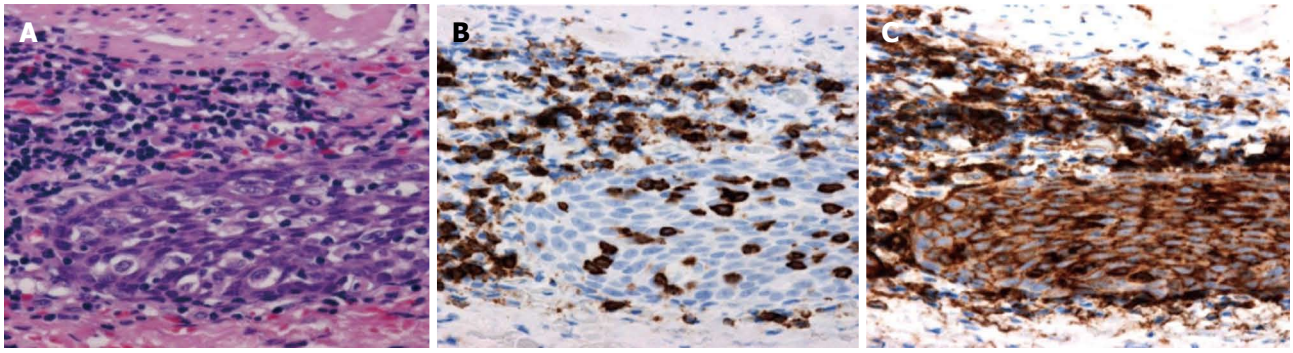

Figure 4 The histopathological findings. A: Poorly differentiated squamous cells and lymphocytes that had infiltrated into the carcinoma cell nests were observed (HE staining, original magnification × 400); B: Prominent infiltration of cytotoxic T lymphoid cells that stained positive for CD8 was observed between and around the carcinoma cells (× 400); C: Strong expression of human leukocyte antigen-DR was evident in the cell membrane in nearly all carcinoma cells and in the lymphocytes around the tumor (× 400).

later. He has been well, without adjuvant therapy or any evidence of recurrence, for more than five years after the surgery. After the diagnosis of the esophageal cancer, he did not smoke or drink alcohol. Furthermore, he did not take any special medicines or examinations.

DISCUSSION

LELC was first reported by Bégin *et al*[8] in 1987. LELC is defined as a tumor with histological similarity to undifferentiated nasopharyngeal carcinoma with lymphoid stroma, and this condition has been described in various organs[1-5]. However, an esophageal LELC is extremely rare. According to the PubMed database, there have been only 21 cases, including the present case, reported in the English-language literature to date[6,9-21]. Our report presents the first case of esophageal LELC that was macroscopically reduced in size.

Burke[22] first detected EBV DNA in gastric cancer that histologically resembled nasopharyngeal lymphoepithelioma, and after that, several reports also demonstrated a close relationship between that type of gastric cancer and EBV. However, there does not appear to be a relationship between esophageal cancer and EBV. In the current case, no relationship between the cancer and EBV was revealed by EBER-1 staining. In addition, we

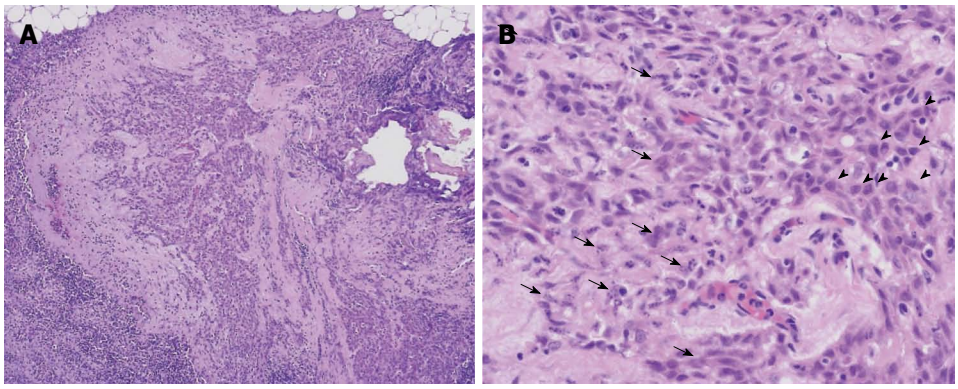

Figure 5 The surgically dissected lymph node from the neck area. A: In the lymph node, which was 5 mm in diameter, a metastasis that was 2 mm in diameter was found (HE staining, original magnification × 40); B: Histological evaluation showed that lymphocytes had infiltrated around the carcinoma cells (HE staining, original magnification × 200). Many denatured carcinoma cells, which had karyorrhexis, an indistinct cell membrane, or karyotheca in the lymph node, were observed (arrow). Many viable carcinoma cells were observed (arrowhead).

investigated 17 of the 21 described patients to determine whether they had an EBV infection. Only three (17.6%) of the 17 described patients were revealed to have an EBV infection. However, Nakasono[20] reported that esophageal LELC may not always be linked with EBV, but that the sensitivity of the detection methods may also be problematic, leading to false-negative findings. Therefore, further investigations are needed to clarify the role of EBV infection in esophageal LELC.

Endoscopically, most cases of LELC have been documented as submucosal tumors covered with normal-appearing esophageal epithelium and with a depression or ulcer in the center of the lesion[6,16,20], as in the present case. However, there has been no previous report of the diagnosis of LELC by endoscopy or biopsy. Because esophageal LELC may be confused with a benign tumor, a biopsy of deeper tissue is required. Moreover, regarding the clinical course, there was a previous report that one year after the first endoscopic examination, the size of the lesion remained unchanged, despite no treatment[20]. However, in our case, the tumor was gradually reduced in size macroscopically and fully disappeared in only 2 mo. It may help the diagnosis of LELC if these endoscopic courses could be followed more closely.

The prominent lymphocytic infiltration in LELC is associated with HLA-DR expression in the deeper carcinoma cells[16]. The T cell infiltration is significantly increased at the sites of HLA-DR expression[23]. In our case, T lymphocytes were found around the lymphoid follicles or within the tumor cell nests, and most of these T cells were positive for CD8, which supports their classification as cytotoxic T lymphocytes.

The role of diffuse infiltrating lymphocytes, consisting of a large number of T lymphocytes and a small number of B lymphocytes, has not yet been clarified in LELC. Two hypotheses have been proposed[13]. In one, the presence of diffuse lymphocytes is explained by the immune response of the host against the carcinoma. In the other, the diffuse lymphocytes are explained in terms of a cell reaction caused by the cytokines produced by the carcinoma cells. In our case, the immune responses against the main tumor and the denatured carcinoma cells in the metastatic lymph node developed at the same time. Therefore, systemic immune responses against the carcinoma might have been occurring. Furthermore, we suppose that the systemic immune response against carcinoma becomes more significant over time and that the tumor becomes smaller when there is increased expression of HLA-DR, as was observed in our case.

Generally, the prognosis of patients suffering from poorly differentiated esophageal squamous cell carcinoma is extremely poor. However, esophageal LELC seems to have a relatively good prognosis[6]. The prognosis is indicated by the survival curves and recurrence rates after treatments. It was fortunate that we could endoscopically follow an LELC lesion that did not receive any treatment for two months because this study helped to demonstrate the natural course of the disease. During this short time, the tumor was gradually reduced in size macroscopically. Histologically, prominent lymphocytic infiltration was revealed in the main tumor and the metastatic lymph node. The patient has remained in good health for the 5 years since the surgery. The immune responses in this case seem to have had nothing to do with his lifestyle. This unique observation was not described in any previous cases.

In conclusion, esophageal LELC has unique clinical and pathological features. In particular, the strength or weakness of the expression of HLA-DR in esophageal LELC may lead to differences in the patient's clinical course. Furthermore, LELC should be treated differently than other esophageal cancers based on its unique features.

COMMENTS

Case characteristics

A 67-year-old male with a 7-mo history of intermittent dysphagia.

Clinical diagnosis

A protruding lesion of 10 mm in diameter was observed on the left and posterior wall of the middle thoracic esophagus.

Differential diagnosis

Malignant lymphoma, gastrointestinal stromal tumor, endocrine cell tumor.

Imaging diagnosis

In only 2 mo, an endoscopic examination revealed that the appearance of the esophageal tumor had changed from a protruding lesion to a flat, scar-like lesion.

Pathological diagnosis

This lesion was considered to be an esophageal lymphoepithelioma-like carcinoma with poorly differentiated squamous cells.

Treatment

After the endoscopic submucosal dissection, a subtotal esophagectomy and dissection of the lymph nodes were performed.

Experiences and lessons

The esophageal lymphoepithelioma-like carcinoma that was macroscopically reduced in size might have occurred due to systemic immune responses against the carcinoma.

Peer review

This is a very interesting case report. Esophageal cancers are quite common in some parts of the world and this report highlights the fact that not all are associated with a dismal prognosis. The report is well written and adequate references. The photographs are very good and illustrative.

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REVIEW

Is peracetic acid suitable for the cleaning step of reprocessing flexible endoscopes?

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Abstract

The bioburden (blood, protein, pathogens and biofilm) on flexible endoscopes after use is often high and its removal is essential to allow effective disinfection, especially in the case of peracetic acid-based disinfectants, which are easily inactivated by organic material. Cleaning processes using conventional cleaners remove a variable but often sufficient amount of the bioburden. Some formulations based on peracetic acid are recommended by manufacturers for the cleaning step. We performed a systematic literature search and reviewed the available evidence to clarify the suitability of peracetic acid-based formulations for cleaning flexible endoscopes. A total of 243 studies were evaluated. No studies have yet demonstrated that peracetic acid-based cleaners are as effective as conventional cleaners. Some peracetic acid-based formulations have demonstrated some biofilm-cleaning effects and no biofilm-fixation potential, while others have a limited cleaning effect and a clear biofilm-fixation potential. All published data demonstrated a limited blood cleaning effect and a substantial blood and nerve tissue fixation potential of peracetic acid. No evidence-based guidelines on reprocessing flexible endoscopes currently recommend using cleaners containing peracetic acid, but some guidelines clearly recommend not using them because of their fixation potential. Evidence from some outbreaks, especially those involving highly multidrug-resistant gram-negative pathogens, indicated that disinfection using peracetic acid may be insufficient if the preceding cleaning step is not performed adequately. Based on this review we conclude that peracetic acid-based formulations should not be used for cleaning flexible endoscopes.

Key words: Peracetic acid; Cleaning; Flexible endoscope; Biofilm; Resistance; Bioburden; Blood; Disinfection; Reprocessing

Core tip: Some formulations based on peracetic acid (PAA) are recommended by manufacturers for cleaning flexible endoscopes. We reviewed 243 studies to analyse the evidence for this recommendation. No study demonstrated that PAA-based cleaners were as effective as conventional cleaners, and some PAA-based formulations had clear biofilm-fixation potential. Dried blood and nerve tissue were substantially fixed by PAA. Some outbreaks, especially of highly multidrug-resistant gram-negative pathogens, indicated that insufficient cleaning could not be compensated for by using PAA in the disinfection step. PAA-based formulations should not be used for cleaning flexible endoscopes.

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INTRODUCTION

Flexible endoscopes come into contact with the mucosa

and are considered as semi-critical equipment, associated with a high risk of infection[1,2]. Infections, including those due to multidrug-resistant gram-negative pathogens, quite frequently occur after gastrointestinal endoscopy[3,4]. The most common types of infections are primary sepsis or bacteraemia[3], pneumonia[3] and gastroenteritis[3], some of which may be fatal. Blood-borne infections such as hepatitis B or hepatitis C have also been described[3]. Most infections are attributed to inadequate cleaning or disinfection of the endoscope before its use on the next patient[3,5,6]. The cleaning process or disinfection step is usually described as inadequate if it deviates obviously from national evidence-based guidelines[7,8].

The processing protocols for flexible endoscopes have changed over the last few decades, with an increase in the popularity of automatic processing[9]. This is associated with advantages such as better standardization, better process validation compared with manual processing[10-17], better overall reprocessing results[18,19] and similar costs[20]. The choice of active disinfection ingredients has increased at the same time. Glutaraldehyde continues to be the main active ingredient in the disinfection step for several decades[21] and is often used for automatic processing at high temperatures such as 56 ℃[22]. It is also used for processing other semi-critical medical devices such as flexible cystoscopes[23], rhinoscopy[24] and bronchoscopes[25]. However, some countries now use peracetic acid-based formulations for the disinfection step[10,14,17,26-30]. Some manufacturers of chemical processing products have recently adapted their processing protocols to recommend the use of peracetic acid-based formulations also for the cleaning step. However, the suitability of peracetic acid for cleaning remains controversial. This study aimed to review the scientific literature on all aspects of the use of peracetic acid-based formulations for cleaning flexible endoscopes, and to provide a clinically relevant summary of the possible implications for patient safety.

STUDY SELECTION

A literature review of the National Library of Medicine was performed on August 19, 2013, using various combinations of the following terms: peracetic acid, cleaning, flexible endoscope, endoscope biofilm, resistance, fixation, infection and outbreak. A total of 471 publications were identified and reviewed for their suitability regarding the topic. A total of 172 studies were considered relevant and evaluated in detail. A further 71 studies not identified by the literature search were also evaluated, *e.g.*, guidelines, reports on side effects, additionally referenced studies or reviews (Figure 1).

STANDARD PROTOCOL FOR PROCESSING FLEXIBLE ENDOSCOPES

Flexible endoscopes are usually processed *via* several steps (Table 1). The cleaning step itself comprises three steps[31]. Pre-cleaning is usually done immediately after use of the endoscope, *e.g.*, with detergent-soaked gauze and rinsing of all channels with the cleaning agents. Pre-cleaning is a standard procedure and may be omitted only under certain conditions[32]. Secondly, brush-cleaning involves cleaning all accessible channels with a brush suited to each channel, and is followed by chemical cleaning, which involves filling all the channels with the cleaning agent for a few minutes, followed by thorough rinsing. The subsequent disinfection step varies in duration, depending on the chemical formulation used and the required spectrum of antimicrobial activity; if virucidal or mycobactericidal activity is required, the duration may be longer. Finally, the endoscope is rinsed once more and dried[33]. Double cleaning is recommended in some countries, such as France, mainly because of the risk of prion diseases[34,35].

The cleaning step itself is considered to be difficult in flexible endoscopes because of the long, narrow lumens and multiple valves[36]. In addition, endoscope channels should be freely accessible, because limited access is associated with significantly poorer cleaning results (approximately 3%)[37]. Manual cleaning is considered less effective than automatic cleaning[38].

IMPORTANCE OF THE CLEANING STEP

There are two major reasons for performing effective cleaning before the disinfection step. First, organic and inorganic materials left on the inner and outer surfaces interfere with the efficacy of the disinfectants[39,40], given that blocked channels may remain undisinfected[41]; only a clean endoscope with clean channels can be disinfected effectively[34]. Second, cleaning of flexible endoscopes aims to reduce the bioburden as much as possible[41]. It is generally acknowledged that the cleaning, rather than the disinfection or sterilization procedure, controls the success of the endoscope[42,43] or angioscopy reprocessing procedure[44] although cleaning alone does not reduce contamination to a safe level[45].

Inadequate cleaning may reduce the efficacy of the disinfection step[46,47] finally leading to contaminated flexible endoscopes after processing, mainly with gram-negative bacteria[48]. Chemical disinfectants work by direct contact between the disinfectant and the microbe, which may be prevented by residual organic material, resulting in incomplete microbial killing[49,50]. Inadequate cleaning was regarded as a main reason in various outbreaks of nosocomial infections associated with bronchoscopy or endoscopic retrograde cholangiopancreatography (ERCP)[51-53]. The importance of optimal cleaning of flexible endoscopes for the overall reprocessing results is acknowledged as a significant issue by physicians and gastroenterology nurses[54].

CLEANING AGENTS

The cleaning agent is usually a detergent without any biocidal ingredient[35]. Some cleaning agents are enzymatic,

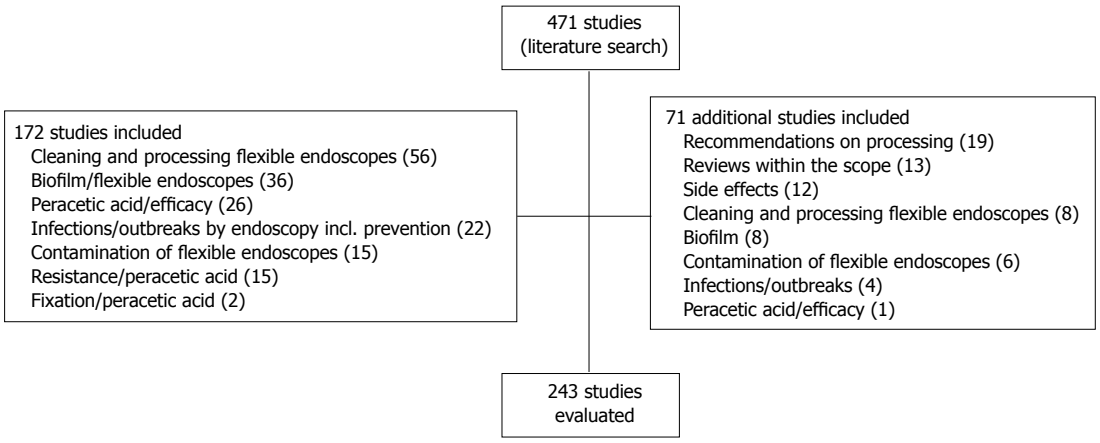

Figure 1 Flow diagram on the study selection process.

Table 1 Typical sequence of steps for manual and automatic reprocessing of flexible endoscopes including the typical duration of the various cleaning steps

Manual processing	Automatic processing
Pre-cleaning the outer surface with a detergent-soaked single-use gauze and rinsing all channels with the cleaning agent, usually for 2 min	
Brush-cleaning all accessible channels with a suitable brush, usually for 3 min	
	Rinsing
Chemical cleaning; filling all channels with the cleaning agent, allowing the cleaning agents to persist inside the channel for approximately 5 min	
Rinsing, usually for 1 min	
Disinfection	
Final rinsing	
Drying	

others are non-enzymatic[55,56]. The cleaning agent should be compatible with the disinfectant agent. The entire process may then achieve a 9 $\log_{10}$ reduction of microorganisms in a tube simulating an endoscope channel[57]. Other processes using different types of cleaning or disinfection agents have revealed lower overall reductions, *e.g.*, a 7 $\log_{10}$ reduction[58]. Lack of use of a detergent in the cleaning step in an automatic processor did not result in any viral blood-borne infections such as hepatitis B or C in 72 patients[59], indicating that the type of cleaning agent is less important in terms of the overall cleaning result for some enveloped blood-borne viruses.

CHEMICAL CHARACTERIZATION OF PERACETIC ACID

Peracetic acid is an oxygen-releasing compound and has been known as a biocidal agent for decades[60-62]. Its current use is mainly for disinfection, *e.g.*, of flexible endoscopes or surfaces[63], sometimes in combination with 1% hydrogen peroxide[64]. In automatic processing of flexible endoscopes, it is used at concentrations of 0.2%[65], 0.35%[66] or even 1%[45], while in manual procedures it may be used at 0.2%[67]. It degrades rapidly to acetic acid and oxygen[68], and its stability is poor compared with glutaraldehyde[69], but may be prolonged by adding stabilizing agents[68]. In common with all oxygen-releasing compounds, it is inactivated by organic materials such as blood[68,70], serum[71,72], albumin[73] or a combination of organic loads[74]. It may be corrosive for a number of materials such as steel or rubber, whereas glass and some plastics are unaffected[68].

FORMULATIONS BASED ON PERACETIC ACID

Various peracetic-acid-based products for processing flexible endoscopes are available in a number of countries; some are powders, and others are liquids used as a one- or two-component system. A number of products available for manual processing are known to the authors and include: Acecide (Saraya Co. Ltd., Osaka, Japan), Gigasept PAA concentrate (Schülke and Mayr, Norderstedt, Germany), neodisher endo DIS active (Chemische Fabrik Dr. Weigert GmbH and Co. KG, Hamburg, Germany), NU Cidex (ASP, Wokingham, United Kingdom), PeraSafe (Antec International Ltd., Sudbury, United Kingdom), Scotalin (KRD, Busan, South Korea), and Sekusept aktiv (Ecolab Inc., St. Paul, MN, United States). Available products for automatic processing include: neodisher Septo PAC (Chemische Fabrik Dr. Weigert GmbH and Co. KG, Hamburg, Germany), Olympus EndoDis (Olympus Europe Holding GmbH, Hamburg, Germany), or Rapicide PA (Medivators Inc. Minneapolis, MN, United States). All these products are described as suitable for the disinfection of flexible endoscopes, but some of them are also recommended by the manufacturer for the cleaning step (Gigasept PAA concentrate, neodisher endo DIS active, and Sekusept aktiv).

PATHOGENS

Pathogens on flexible endoscopes after use

The total contamination of flexible endoscopes with pathogens is usually highest in colonoscopes, followed by gastroscopes and bronchoscopes[75]. The microbial load

after patient examination was found to be between > 10^3 and 10^{10} colony-forming units (CFU) per milliliter[48,76], with highest numbers in the suction channel[77-79]. The contamination consisted mainly of gram-negative bacteria (56%) such as *Pseudomonas aeruginosa*, *Klebsiella pneumonia* and *Escherichia coli*, followed by gram-positive bacteria (27%) such as *Staphylococcus aureus*, coagulase-negative *Staphylococcus* and *Micrococcus luteus,* and yeasts (17%) such as *Candida albicans* and *Candida tropicalis*[48]. The air and water channels may, however, also be contaminated[80]. If biopsy suction channels are not adequately cleaned, remaining pathogens may contaminate single-use sterile biopsy forceps during passage[81,82].

Infected patients leave their infectious flora on the endoscope. Hepatitis B virus DNA, hepatitis C virus RNA, human immunodeficiency virus DNA and *H. pylori* have been found after use of endoscopes in infected patients[83-86], especially in the biopsy suction channel[87], and even after cleaning[88]. It is estimated that, on average, 4 in every 1000 endoscopies result in transmission of *H. pylori*[89].

Pathogens on flexible endoscopes after cleaning

The cleaning step can reduce the bioburden by 4.7 $\log_{10}$ CFU (gastroscopes) and 6.2 $\log_{10}$ CFU (colonoscopes)[76,90]. Automatic cleaning and manual cleaning resulted in a similar reduction in microbial load (4.32 and 4.24, respectively), when measured with *E. faecalis* and *P. aeruginosa*[33]. *M. chelonae* may be reduced by 4 $\log_{10}$-steps by standardized manual cleaning[91]. Automatic cleaning processes may achieve a $\log_{10}$-reduction of 7.0-8.4, depending on the type of washer disinfectant and cleaning agent[92].

In contaminated test tubes the cleaning step during automatic processing of flexible endoscopes shows variable results, depending on the type of process and the cleaning agent[58]. Some cleaning processes using a detergent were significantly less effective (0.3 $\log_{10}$-steps) than water alone (1.1-2.6 $\log_{10}$-steps), indicating that the entire cleaning process needs to be evaluated critically[55,56]. In contrast, other cleaning processes were significantly more effective (4.1 $\log_{10}$-steps)[56].

HCV is usually completely removed from the biopsy suction channel by the cleaning step alone, as demonstrated in 19 upper gastrointestinal endoscopic procedures in patients with chronic replicative hepatitis C[85]. This finding is supported by *in vitro* data using contaminated high-titre HCV-positive plasma for experimental contamination of flexible endoscopes[93], and by evaluation of flexible endoscopes used in patients with hepatitis C[94]. HIV was a also reduced by at least 99.93% using a detergent cleaning step alone[95].

Overall cleaning effectively reduces or eliminates many pathogens by at least 4 log as recommended[77], but substantial levels of viable bacteria may remain[78]. This suggests that the risk of transmission of nosocomial pathogens cannot be eliminated by cleaning alone[96]. Poor mechanical cleaning may be indicated by a high titre of microorganisms in a surveillance culture[97].

Effect of peracetic acid on pathogens

Antimicrobial activity: Peracetic acid is very reactive and has strong antimicrobial activity. Depending on its concentration and pH value[98], it is effective against bacteria including *H. pylori*, fungi, mycobacteria, viruses including hepatitis B virus, and bacterial spores[35,66,68,99-112], though for specific isolates, such as *Mycobacterium gordonae*, the exposure time may have to be prolonged to 20 min to achieve the required efficacy[67]. However, despite its broad spectrum of antimicrobial activity it is not suitable for sterilizing surgical instruments[113]. In combination with copper, peracetic acid is also considered to be suitable for prion decontamination[114]. The optimal pH value for its antimicrobial activity is between 2.5 and 4[68]. It is also assumed that exposure of gram-positive species such as *Bacillus subtilis* to chlorine dioxide enhances a stable cross-resistance to other oxidizing agents, such as peracetic acid[74], as confirmed by Bridier *et al*[115]. The efficacies of different formulations differ remarkably compared with solutions of the active ingredient alone[116].

Cellular changes to sublethal concentrations: Bacterial resistance to biocides is apparently increasing, although peracetic acid has not been implicated in the selection and persistence of bacterial strains with low-level antibiotic resistance[117]. Exposure of nosocomial pathogens to peracetic acid at a sublethal concentration (*e.g.*, 1 mmol/L) has been reported to induce a cellular response in *S. aureus*. This response includes the induction of many virulence-factor genes upon exposure, suggesting stimulation of pathogenesis in response to peracetic acid[118]. Other effects included significant alterations in the regulation of membrane-transport genes, selective induction of DNA-repair and -replication genes, and differential repression of primary metabolism-related genes between the two growth states[118]. Similar reactions were observed after exposure of *P. aeruginosa* to a sublethal concentration (*e.g.*, 1 mmol/L) of peracetic acid: many genes associated with cellular protective processes were induced, while transcription of genes involved in primary metabolic pathways was repressed, and that of genes encoding membrane proteins and small molecule transporters was altered[119]. In terms of *E. coli* O157:H7, a sublethal concentration of peracetic acid (0.1%) induced a substantial increase in peroxidative tolerance[120]. Finally, a strain of *Salmonella typhimurium* exposed to a sublethal concentration of peracetic acid (*e.g.*, 15 mg/L) showed modified physiological characteristics: the cells remained viable but were unable to be cultured, but retained their virulence, as shown by their adhesive and invasive capacities[121]. A higher concentration of peracetic acid (*e.g.*, 20 mg/L) resulted in bacterial death. This study indicated that a negative culture result from an endoscope does not exclude the presence of pathogens on the endoscope, and transmission may occur if the bacterial cells modify their physiological characteristics, *e.g.*, by exposure to sub-

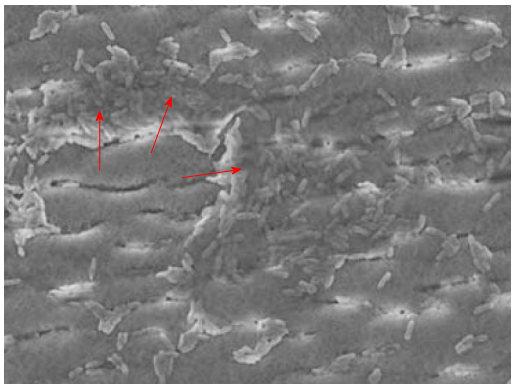

Figure 2 Residual biofilm after exposure to 0.09%-0.15% peracetic acid, as shown by Balsamo *et al*[141]. Reproduced by kind permission of the publisher.

lethal concentrations of peracetic acid.

BIOFILM

General background

Biofilms are communities of cells that are attached to an abiotic or living surface embedded in an extracellular polymeric substance[122,123]. They are preferentially formed in wet environments (*e.g.*, insufficient drying of endoscopes before storage[124,125]), can form under different flow conditions[126,127] and can be potential sources of contamination and infection[128]. Virtually all bacterial species can form biofilm including clinically-relevant ones such as *P. aeruginosa*, *S. aureus*, *E. coli* and *Clostridium difficile*[123,129,130]. Under natural environmental conditions, biofilms are likely to be composed of a mixture of different species[131,132]. In the laboratory, they can be grown on various materials and devices, including polystyrene microtitre plates[133-136], haemolysis glass tubes[137,138], stainless steel coupons[134,139] and also in Teflon tubes[140-143], similar to endoscope channels.

Resistance of biofilm bacteria

One feature of many biofilm bacteria is their resistance to some antibiotics and disinfectants ([144-147] and reviewed in[148,149]). Artificial *P. aeruginosa* biofilms resisted treatment with various biocidal agents including peracetic acid, compared with their planktonic counterparts[150-152]. Biofilms composed of *E. coli*[152,153], *S. aureus*[152,154,155], *Mycobacterium fortuitum*[156] or *Listeria monocytogenes*[157] also resisted treatment with diverse biocides compared with planktonic cells. Bacteria in mature (old) biofilms were more resistant to killing than those in young biofilms[153,158,159]. An older biofilm of *P. aeruginosa* required up to 20-fold higher concentrations of peracetic acid (0.2%) to be eradicated, compared with their planktonic counterparts (0.01%)[151]. Similar results were found with an *E. coli* biofilm and peracetic acid/H_2O_2[153]. The resistance of biofilms can often further increase when the communities are composed of more than one bacterial species[134,136,160-163] which may include resistance against 0.35% peracetic acid, which is a concentration used in many formulations[133]. Especially "build-up" biofilms mimicking repeated endoscope reprocessing cycles exhibited a significantly higher survival rate than 'traditional' biofilms[158]. The mechanisms underlying disinfectant-resistant phenotypes appear to be multifactorial[133,148,151,153,164].

Biofilm on flexible endoscopes

Direct evidence for extensive biofilm contamination was provided in 1 of 13 investigated biopsy suction channels and 5 of 12 air/water channels of reprocessed endoscopes[165]. Some reports showed persistent levels of bacteria in endoscope channels, despite reprocessing according to published guidelines, providing indirect evidence for contamination by biofilms[166-168]. Residual biofilm can be seen in Figure 2. In one case, a colonoscope was contaminated with a total of 195 bacteria despite six rounds of reprocessing[168]. Treatment with a cleaning agent that had previously been shown to remove biofilms from endoscope tubes[142] was capable of eradicating the microbes almost completely, indicating that the presence of biofilm was the main reason for ongoing bacterial contamination[168]. Biofilms were also found in washer disinfectors resulting in contamination of automatically-processed endoscopes, *e.g.*, with *Mycobacterium chelonae*[169,170], *Methylobacterium mesophilicum*[170] or *P. aeruginosa*[171], some giving rise to nosocomial infections[171]. Biofilm formation and fixation should therefore also be avoided in washer disinfectors[172]. If biofilms are not thoroughly removed from endoscope channels by cleaning, subsequent disinfection might fail, enabling microorganisms to persist. Further, efficient interchange of plasmids might occur in biofilms, including those coding for antibiotic resistance such as cefotaxime- or aminoglycoside-resistance[173-176].

Biofilm on flexible endoscopes after cleaning

Shear stress was found to remove some biofilms, though 24% and 47% of the biofilm masses, respectively, remained attached[177]. Brushing a silicone tube 10 times with a sterile brush was found to completely remove a multispecies biofilm that had developed over a period of 50 d[178].

Commercial detergents show variable results on biofilm removal[179]. A non-enzymatic detergent yielded a significantly higher $\log_{10}$-reduction (4.13 to 4.17 $\log_{10}$-reduction) of residual wall *E. coli* biofilm bacteria than the enzymatic detergents (0.74 to 0.88 $\log_{10}$-reduction), whilst contact time (3, 5 or 7 min) had no significant impact[180]. Similar results on different cleaners were reported by Fang *et al*[181] and Vickery *et al*[182]. Quantification of endotoxin levels also revealed better results for a non-enzymatic cleaner in terms of biofilm reduction[183]. A non-enzymatic cleaner continued to remove more biofilm with an increasing number of wash/contamination cycles: by the 20th cycle, 90% of the tubing was biofilm-free[184].

New cleaning formulations based on phosphates, hydrates, minerals and surfactants were developed several

years ago[142]. These formulations effectively removed multispecies biofilms from Teflon tubes, prevented the growth of new biofilms in endoscopes, and established biofilms were completely removed from endoscopes by sequential washing with an enzymatic solution and a bleach-enriched version of the new cleaning formulations[142]. Three repeats of a reprocessing of more than 1 h using sequential application of these cleaning components almost completely removed biofilms from flexible endoscopes that had been used in patients, and were persistently contaminated with bacteria despite six rounds of reprocessing[168]. The practicality of this procedure, however, remains doubtful.

Effect of peracetic acid on biofilm

Treatments with aldehyde, peracetic acid plus detergent, or chlorine failed to disturb or remove biofilm, despite a significant log reduction in biofilm bacteria[178]. Biofilm in a water line in a dental unit with permanent water contact was effectively removed by a peracetic acid flush (0.26%)[185], but this has no correlate in endoscope processing. *P. aeruginosa* biofilms remained in an endoscope prototype in 76.2% of tested tube segments after cleaning followed by manual peracetic acid (0.09%-0.15%) processing and in 23.8% after cleaning followed by automatic peracetic acid processing[141]. The same processes with glutaraldehyde (2%) revealed lower rates of 71.4% after manual processing and 4.8% after automatic processing[141]. Protein in a *P. aeruginosa* biofilm could be removed by peracetic acid by 41%. The removal is much lower from mature biofilms or biofilms subjected to repeated peracetic acid treatments, which may modify biofilm structure[143]. At the same time, the biofilm was partially fixed and accumulated after exposure to two peracetic acid-based formulations[143]. Fixation rates varied between formulations within the same chemical group[143]. Four peracetic acid-based products were reported, two of which fixed artificial biofilms quite strongly, while the other two containing additional quaternary ammonium compounds showed no biofilm fixation[138]. An *E. coli* biofilm exposed to three different peracetic acid-based formulations (one with peracetic acid, one with additional non-ionic surfactant, and one with additional cationic surfactant) was partly removed by two formulations, and not fixed by any of the three formulations[137].

Finally, sublethal concentrations of chlorine dioxide, an active compound used for disinfection of endoscopes, *may accelerate* formation of *B. subtilis or P. aeruginosa biofilms* compared with biofilms grown in the absence of chlorine dioxide[186]. A similar effect can be expected with other oxygen-releasing compounds.

BLOOD

Blood on flexible endoscopes after use

Contamination of flexible endoscopes with blood is to be expected, *e.g.*, after biopsy or in the case of variceal gastrointestinal bleeding. It is also common in other types of endoscopic procedures[187]. After different types of endoscopic procedures, suction channels contain haemoglobin at a concentration of 85 μg/cm^2[78]. Residual blood may contain blood-borne viral pathogens[83,84,87,88] and may impair the efficacy of the subsequent disinfection step[44,68,70,188].

Blood on flexible endoscopes after cleaning

Detergent-based formulations are capable to remove between 88% and 95% of dried blood while peracetic acid-based formulations only removed 8%-59% depending on the type of formulation[183,189]. These results indicate that dried blood is not removed as easily by peracetic acid-based formulations compared with detergent-based formulations.

Effect of peracetic acid on blood

At the same time, however, the rate of fixation of blood exposed to the same peracetic acid-based formulations was between 19% and 78%[189], indicating that the remaining blood is fixed and cannot be easily removed. A similar effect can be seen on clinically used endoscopes containing organic contamination fixed by glutaraldehyde disinfectant solution: 20 cleaning cycles using a buffered peracetic acid procedure removed 30%-50% of the contamination[190]. These data highlight the need to avoid contact between organic contaminant and agents with fixation properties, because subsequent removal may be difficult.

OTHER ORGANIC CONTAMINATION

Organic contamination on flexible endoscopes after use

Suction channels may contain proteins at a concentration of 115 μg/cm^2 after endoscopic procedures[78].

Organic contamination on flexible endoscopes after cleaning

Organic contamination may remain after cleaning. It was reported that 95 out of 504 samples obtained before disinfection and tested for adenosine triphosphate were above the benchmark values (200 relative light units [RLUs])[191], indicating inadequate cleaning[192]. Levels may be as high as 10417 RLUs on the exterior endoscope surface, or 30281 RLUs on the biopsy suction channel rinsates[193].

Haemoglobin and protein may also remain after cleaning. A channel is considered clean if the haemoglobin level is < 2.2 μg/cm^2 and the protein level is < 6.4 μg/cm^2[194]. If all these parameters are fulfilled, the ATP level will be < 200 RLUs[191] which can be considered a validated benchmark from patient endoscopes[195].

Overall, most of the organic contamination is usually removed below benchmark by detergent-based cleaning procedures, although exceptions may occur[196].

Effect of peracetic acid on organic contamination

Peracetic acid used for high-level disinfection of duo-

Table 2 Outbreaks and pseudo-outbreaks reported in connection with biofilm or peracetic acid-based processing of flexible endoscopes

Number/type of infection(s)	Pathogen(s)	Type of endoscopic procedure	Reason for outbreak / pseudo-outbreak	Peracetic acid-based formulations were used for	Ref.
None (pseudo-outbreak)	*Pseudomonas aeruginosa*	Gastroscopy, bronchoscopy	Suboptimal duration of glutaraldehyde application during disinfection; "resistance" to glutaraldehyde may have been enhanced by manual cleaning with peracetic acid-based disinfectant[214]	Cleaning step	[202]
2: infection (not further specified) 3: colonization	OXA-48 *Klebsiella pneumoniae*	Bronchoscopy	A problem with the washer disinfector or the cleaning procedure was assumed as the reason	Cleaning step and disinfection step (Gastmeier P, personal communication)	[203]
4: pneumonia (3 cases); colonization (1 case)	MDR *Pseudomonas aeruginosa*	Gastroscopy	Insufficient initial cleaning, shortening of the immersion time and brushing time, insufficient channel flushing, and inadequate drying prior to storage	Disinfection step	[124]
4: bacteraemia, biliary tract infection, respiratory tract infection 9: colonisation	KPC-2 *Klebsiella pneumoniae*	Duodenoscopy	Contaminated duodenoscope; reason for outbreak: inadequate cleaning	Disinfection step	[204]
8: bloodstream infection 4: biliary tract infection 4: colonization	ESBL *Klebsiella pneumoniae* (CTX-M-15)	ERCP	Insufficient manual cleaning, insufficient drying after processing	Disinfection step	[125]
3: sepsis	*Pseudomonas aeruginosa*	ERCP	Presence of biofilm on undamaged channels	Disinfection step (Kovaleva J; personal communication)	[205]
5: infection (not further specified) 9: colonization	OXA-48 *Klebsiella pneumoniae*	Duodenoscopy	One endoscope had probably a defect resulting in insufficient disinfection	Disinfection step (Gastmeier P, personal communication)	[203]
18: pulmonary infection (4 cases, one of them died); colonization (14 cases)	Imipenem-resistant *Pseudomonas aeruginosa*	Bronchoscopy	Incorrect connectors joining the bronchoscope suction channel to the STERIS SYSTEM 1 processor	"Automatic processing"	[206]
2: bacteremia and biliary tract infection 4: colonization	KPC-2 *Klebsiella pneumoniae*	Gastroscopy	Delayed pre-wash resulting in drying of the gastroscope; short drying period after the peracetic acid treatment resulting in incomplete drying	"Wash"	[207]

ERCP: Endoscopic retrograde cholangiopancreatography.

denoscopes yielded significantly lower levels of protein (4.2 μg/mL *vs* 10.1 μg/mL), carbohydrate (18.5 μg/mL *vs* 111.1 μg/mL) and endotoxin (2.8 EU/mL *vs* 44.5 EU/mL) in the biopsy suction channels compared with processes using glutaraldehyde[197]. Despite the differences between the two active agents used only for the disinfection step, the authors concluded there may be a cumulative build-up of organic material components on the inner lumen of the biopsy suction channels of endoscopic retrograde cholangiopancreatography scopes in use[197]. An outbreak of eight fatal cases of *Serratia odorifera* septicemia was caused by contaminated parenteral nutrition fluid due to inadequate cleaning of the surfaces prior to the use of peracetic acid[198]. Dialyzers cleaned with peracetic acid showed significantly lower clearance of larger dextrans as a result of the presence of residual proteins on or within the membrane[199]. Similar findings were reported with a product containing hydrogen peroxide and peroxyacetic acid, compared with one containing sodium hypochlorite[200].

Special case: effect of peracetic acid on nerve tissue

Exposure of brain homogenate to peracetic acid (1500 ppm for 20 min) is associated with a very high protein fixation rate of 96%, which is much higher than with exposure to glutaraldehyde (19%)[201]. Mice inoculated with variant Creutzfeld-Jacob disease (vCJD)-infective brain homogenate previously exposed to peracetic acid survived on average 291 d, which was significantly shorter than mice inoculated with negative control homogenate (> 450 d). Mice inoculated with vCJD-infective brain homogenate previously exposed to glutaraldehyde (2% for 20 min) survived longer compared with the peracetic acid group (mean: 324 d), demonstrating a clinical correlate of the almost complete fixation of brain homogenate protein by peracetic acid[201].

OUTBREAKS AND PSEUDO-OUTBREAKS

Outbreaks and pseudo-outbreaks connected with peracetic acid-based processing of flexible endoscopes are summarized in Table 2. In some outbreaks peracetic acid was used for the cleaning step[202], the cleaning and disinfection step[203], the disinfection step[124,125,203-205] or generally for processing/washing[206,207]. The reasons for the infections were insufficient (initial) cleanin[124,125,202-204], inadequate drying prior to storage[124,125,207], shortening of the immersion time and brushing time[124], insufficient channel flushing[124], a problem with the washer disinfec-

Table 3 Adverse effects after processing with peracetic acid after endoscopy

Number of cases	Type of reaction	Possible explanation	Ref.
10	Colitis	Unclear, reprocessing with PAA, but afterwards channels were flushed with hydrogen peroxide	[210]
1	Colitis	PAA residues in the biopsy suction channel	[215]
2	Colitis	Defect of automatic rinsing of a channel	[216]
1	Colitis	Channel not flushed	[217]
1	Colitis	Inadequate rinsing of a channel	[212]
No number provided	Pseudolipomatosis	Air channels not rinsed	[218]
4	Colitis	Programming error in the automatic disinfection device, related to the air/water channels	[219]
12	Colonic mucosal pseudolipomatosis	Rinsing was not done as recommended	[220]

Table 4 Overview of evidence-based guidelines for processing flexible endoscopes, focusing on the use of peracetic acid during the cleaning step

Institution	Guidelines	Year	Use of peracetic acid for cleaning
AORN	Recommended practices for cleaning and processing endoscopes and endoscope accessories[221,222]	2012	No recommendation
APIC	APIC guidelines for infection prevention and control in flexible endoscopy. Association for Professionals in Infection Control[223]	2000	No recommendation
APSIC	The ASEAN Guidelines for disinfection and sterilization of instruments in health care facilities[224]	2012	No recommendation
ASGE	Multisociety guidelines on reprocessing flexible gastrointestinal endoscopes: 2011[225,226]	2011	No recommendation
BC Ministry of Health	Best Practice Guidelines For Cleaning, Disinfection and Sterilization of Critical and Semi-critical Medical Devices[227]	2011	No recommendation
BSG	BSG Guidelines for Decontamination of Equipment for Gastrointestinal Endoscopy[228]	2008	No recommendation
CDC	Guidelines for Disinfection and Sterilization in Healthcare Facilities, 2008[229]	2008	No recommendation
ESGE/ESGENA	ESGE/ESGENA Technical Note on Cleaning and Disinfection[230][1]	2003	**Recommended**
ESGE/ESGENA	ESGE-ESGENA guideline: Cleaning and disinfection in gastrointestinal endoscopy, update 2008[231]	2008	No recommendation
HPS	Endoscope Reprocessing: Guidance on the Requirements for Decontamination Equipment, Facilities and Management[232]	2007	No recommendation
JGETS	Guidelines for cleaning and disinfecting endoscopes - Second edition[233]	2004	No recommendation
Public Health Agency of Canada	Infection Prevention and Control Guideline for Flexible Gastrointestinal Endoscopy and Flexible Bronchoscopy[234]	2010	No recommendation
RKI	Hygiene requirements for reprocessing of medical devices[235][2]	2001	No recommendation
RKI	Hygiene requirements for reprocessing of medical devices[236]	2012	**Not recommended**
SGNA	Standards of Infection Control in Reprocessing of Flexible Gastrointestinal Endoscopes[237]	2013	No recommendation
WGO/OMED	WGO/OMED Practice Guideline Endoscope Disinfection[238]	2005	**Recommended**
WGO/WEO	Endoscope disinfection - a resource-sensitive approach[239]	2011	No recommendation

[1]These guidelines were updated in 2008 by guidelines[231]; [2]These guidelines were updated in 2012 by guidelines[236]. AORN: Association of periOperative Registered Nurses; APIC: Association for Professionals in Infection Control and Epidemiology; APSIC: Asia Pacific Society of Infection Control; ASGE: American Society for Gastrointestinal Endoscopy; BSG: British Society of Gastroenterology; CDC: Centers for Disease Control and Prevention; ESGE: European Society of Gastrointestinal Endoscopy; ESGENA: European Society of Gastroenterology and Endoscopy Nurses and Associates; HPS: Health Protection Scotland; JGETS: Japanese Gastroenterological Endoscopy Technicians Society; OMED: Organisation Mondiale d'Endoscopie Digestive/World Organization for Digestive Endoscopy; RKI: Robert Koch Institute; SGNA: Society of Gastroenterology Nurses and Associates, Inc; WEO: World Endoscopy Organization (former OMED); WGO: World Gastroenterology Organisation.

tor[203], presence of biofilm on undamaged channels[205], an endoscope defect[203], delayed pre-wash resulting in drying of the gastroscope[207], and incorrect connectors joining the bronchoscope suction channel to the STERIS SYSTEM 1 processor[206]. Strict adherence to infection control guidelines for reprocessing endoscopes is therefore the key element for prevention of endoscope-associated outbreaks[203].

CLINICAL SIDE EFFECTS OF PERACETIC ACID

The potential health risks associated with all high-level disinfectants are considered to be serious, though little is known about the risks to humans, especially employees, from glutaraldehyde alternatives[208,209]. Gutterman *et al*[209] identified only eight studies "which reported numerous adverse outcomes to healthcare personnel associated with endoscope reprocessing", including one case report with asthma for workers using a peracetic acid and hydrogen peroxide based product. The most commonly-reported side effect of peracetic acid in patients is a form of colitis, previously known as pseudolipomatosis[210], which is commonly induced by hydrogen peroxide and peracetic acid but occasionally also by glutaraldehyde[211]. The colitis is often self-limiting but sometimes requires medical treatment. The frequency of colitis caused by peracetic

Table 5 Effects and possible outcomes of peracetic acid use for cleaning flexible endoscopes

Characteristic, reason for cleaning step	Effect of peracetic acid	Possible outcome, compared with classical cleaning
Removal of biofilm	Variable[1]	Insufficient removal of biofilm
Fixation of biofilm	Possible[1]	Fixation of biofilm to variable degrees
Removal of dried blood	Partial removal[1]	Insufficient removal of dried blood
Fixation of dried blood	Very likely	Fixation of dried blood to variable degrees
Fixation of brain tissue	Very likely	Strong fixation of nerve tissue, including prions
Adaptation of microorganisms surviving the cleaning step	Likely, especially in gram-negative bacteria	Insufficient efficacy of disinfection step, persistence of pathogens, beginning of biofilm formation
Cross-resistance to other biocidal compounds as a result of exposure to sublethal peracetic acid concentrations	Possible	Insufficient efficacy of disinfection step, persistence of pathogens, beginning of biofilm formation

[1]Depending on the formulation.

acid might be underestimated[212]. An overview of all reported cases is summarized in Table 3.

REVIEW OF NATIONAL AND INTERNATIONAL GUIDELINES

An overview of 17 guidelines from 14 different institutions is given in Table 4. Most institutions make no statement on the suitability of peracetic acid for cleaning flexible endoscopes, but there seems to be a recent trend in a few institutions to either skip their earlier recommendations of peracetic acid (ESGE/ESGNA and WGO/WEO) or to state that it is not suitable for cleaning (RKI).

CONCLUSION

Few national and international guidelines highlight the need for the cleaning of flexible endoscopes to be carried out using formulations without any fixation potential, but use of peracetic acid for cleaning is discouraged. Some peracetic acid-based formulations have some cleaning capacity. However, we found no conclusive evidence to suggest that the cleaning capacity of any peracetic acid-based formulation was as good as that of detergent-based cleaning agents without biocidal agents. Different peracetic acid-based formulations have been shown to enhance surface fixation of dried blood (all tested formulations), biofilm (some tested formulations) and brain tissue (all tested formulations). Fixed blood and biofilm are likely to impair the efficacy of the disinfection step, given that peracetic acid is known to lose its antimicrobial activity in the presence of various types of organic load. Fixed biofilm will reduce the susceptibility of microorganisms present in the biofilm, making it more difficult to achieve the required log-reduction during the disinfection phase. Even if the bacteria within a biofilm are killed by a disinfectant, microorganisms are likely to adhere to any residual biofilm structure within the endoscope more easily during the next endoscopic procedure.

Table 6 Practical tips to ensure optimal cleaning of flexible endoscopes

Clinical practice tip	Major advantage	Ref.
Clean promptly after use	No drying of organic material such as blood	[77,207]
Follow the instructions of the endoscope manufacturer as closely as possible (*e.g.*, type of brush or cleaning adapter)	Optimum cleaning of an entire channel	
Prefer washer disinfectors with a monitoring system indicating channel blockage	A blocked channel cannot be cleaned adequately and is immediately identified; targeted brush cleaning may be necessary	
Do not switch off the monitoring system for detection of blocked channels	Channels may be blocked and inadequately cleaned; personnel may not detect blocked channels with all possible implications for patient safety	
Support by gastroenterologist	It is strongly recommended that the clinician fully understands the cleaning and disinfection steps and does not inhibit his or her staff's ability to perform them correctly	[240]
Allow external audits by local health authorities on the quality of processing including cleaning	Implementation of guidelines may be more successful if the local health authorities visit the endoscopy units and compare current practices with the relevant guidelines. This effect seems to be more easily achieved in in-patient rather than in out-patient endoscopy units	[241-243]

Published research suggests that peracetic acid-based agents are not suitable for use in the cleaning step during the processing of flexible endoscopes (Table 5). However, some practical tips may help to improve the quality of the cleaning step (Table 6). This review highlights that protocols for processing flexible endoscopes should be evidence-based, rather than being based on convenience[213].

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REVIEW

Recent trends in endoscopic management of achalasia

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Abstract

Esophageal achalasia is a chronic and progressive motility disorder characterized by absence of esophageal body peristalsis associated with an impaired relaxation of lower esophageal sphincter (LES) and usually with an elevated LES pressure, leading to an altered passage of bolus through the esophago-gastric junction. A definitive cure for achalasia is currently unavailable. Palliative treatment options provide only food and liquid bolus intake and relief of symptoms. Endoscopic therapy for achalasia aims to disrupt or weaken the lower esophageal sphincter. Intra-sphincteric injection of botulinum toxin is reserved for elderly or severely ill patients. Pneumatic dilation provides superior results than botulinum toxin injection and a similar medium-term efficacy almost comparable to that attained after surgery. Per oral endoscopic myotomy is a promising option for treating achalasia, but it requires increased experience and further objective and long-term follow up. This article will review different endoscopic treatments in achalasia, and summarize the short-term and long-term outcomes.

Key words: Achalasia; Endoscopy; Pneumatic dilation; Botulinum toxin injection; Per oral endoscopic myotomy; High resolution manometry; Dysphagia

Core tip: No definitive treatments of achalasia are currently available. Palliative treatment options aims to relieve symptoms and to help patients for food and liquid intake. Endoscopic approach to achalasia is directed to disrupt or weaken the lower esophageal sphincter. On the other hand, intra-sphincteric injection of botulinum toxin is reserved for elderly or severely ill patients. Pneumatic dilation provides better results than botulinum toxin injection and a clinical benefit comparable to surgery. Per oral endoscopic myotomy is a promising option but it requires increased experience and further objective and long-term follow up.

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INTRODUCTION

The term "achalasia" (from the Greek "alfa" and "chalasis", words for absence of relaxation) was introduced by Lendrum in 1937[1]. Before that and since then, a host of other names have been used, including achalasia cardiae, cardiospasm, and esophageal aperistalsis, reflecting the key physiological abnormalities of the

disease. The incidence of achalasia is expected to be 1 in 100000 persons per year with a prevalence of 10 in 100000. This disorder can appear at any age, with a two peaks incidence at 20-40 and 70-80 years, without gender prevalence[2]. Esophageal achalasia has been credited to a loss of myenteric plexus ganglionic cells in the esophagus, but its cause remains uncertain[3,4]. Achalasia is characterized by the absence of esophageal body peristalsis associated with an impaired relaxation of the lower esophageal sphincter (LES), and usually with an elevated LES pressure[5,6]. Obviously, these features lead to a failure in the passage of bolus through the esophagogastric junction. The predominant symptom in most patients with achalasia is dysphagia, often for both solids and liquids, or "paradoxical" (first for liquids, then for solids) as a distinction from organic dysphagia. Other symptoms often reported are listed as regurgitation, chest pain, heartburn, and weight loss. Patients with achalasia may also present with symptoms such as slow eating or "augmenting pressure" manoeuvres, to allow a bolus passage through gastric cardia; this may hesitate in delaying medical examination, with a progressive dilation of esophageal lumen[7]. Patients who are suspected to be affected by achalasia commonly require endoscopy, barium esophagram and esophageal manometry for diagnosis[8]. Endoscopic evaluation of the esophagus and stomach must rule out a malignancy or a stenosis causing dysphagia. In achalasia patients, it is common to detect a dilation of esophageal lumen, with food deposit and fluid collection; tight LES appears to be tight and passage through the esophago-gastric junction with the endoscope is perceived as a "pop" opening. Nevertheless, a common esophagus appearing at upper endoscopy can be found, because up to 40% of patients with early-stage disease will have an apparent lack of dilated esophagus[9]. On barium esophagram, achalasia is characterized by the presence of a dilated esophagus, absence of peristalsis, and an impaired passage at the esophagogastric junction, associated with symmetric, smooth narrowing of the region ("bird's beak" sign). Accumulation of barium is seen in the body of the esophagus, especially in patients with huge dilation and curvature of the lower esophagus[10]. Although endoscopic examinations and esophagography currently play an important role in the diagnosis, esophageal motility evaluation by means of manometry is considered the "gold standard" test for achalasia. Classically, at standard esophageal manometry, achalasia is diagnosed when esophageal body peristalsis is totally lacking (absence), often associated to a LES resting pressure > 45 mmHg (hypertensive) and a poorly relaxing LES (residual pressure > 8 mmHg)[11]. Recently, high-resolution manometry (HRM) has been introduced as a new technique for the evaluation of esophageal motility disorders. HRM uses 1 cm spaced pressure sensors spanning thorough the whole esophagus, distal pharynx and proximal stomach, enabling the motility to be displayed as concrete colour images. The new Chicago classification has been proposed to classify esophageal motility disorders on HRM. Achalasia is now organized into 3 types (Ⅰ, Ⅱ and Ⅲ) according to the esophageal motor function[12]. In particular, "classic achalasia" (Type I) appears as a peristaltic esophagus with no distal increase in pressure > 30 mmHg; "achalasia with pan-esophageal compression", or type Ⅱ, has to show at least 20% of liquid swallows with a body pressurization > 30 mmHg, and "spastic achalasia" (type Ⅲ) is described when at least 20% of liquid swallows appears to be spastic contractions, associated or not to a pressurization. In this study, the authors showed that achalasia with pan-esophageal compression was associated with a better symptom response and a lower necessity to undergo several treatments than the other 2 types. A definitive cure for achalasia is currently unavailable. Palliative treatment options provide only transit of food and liquid bolus through the gastroesophageal junction, thereby relieving feeding and symptoms. These treatments include drug therapy, endoscopic botulinum toxin injection (BTI), endoscopic pneumatic dilation (PD), per oral endoscopic myotomy (POEM), and surgical extramucosal myotomy, with or without an anterior, posterior or total fundoplication. This article will review different endoscopic treatments in achalasia, and summarize the short-term and long-term outcomes.

ENDOSCOPIC BOTULINUM TOXIN INJECTION

Botulinum toxin can impede the release of acetylcholine from cholinergic neurons. Chemical denervation after an injection of botulinum toxin is intended to lower both basal and residual LES pressure, therefore reducing bolus obstruction[13,14]. Usually, an endoscopic needle is used to inject 20 to 25 units of botulinum toxin into quadrants, at the squamocolumnar junction or up to 1 cm proximally, for a total dose of 80 to 100 units. Recommendations are given to inject the toxin equally in a circumferential manner and at the same level, avoiding submucosal injection or injection outside the esophageal wall. Different authors proposed alternative solutions to improve outcomes, such as injecting by means of endoscopic ultrasound or using different types of botulinum toxin, but these remained only experimental practices[15]. Commonly, 70%-80% of patients referred showed relieved or improved symptoms within 30 d after the procedure.

After BTI, patients occasionally referred transitory non-cardiac chest pain and only those who experienced a beneficial effect of the toxin rarely reported reflux. Severe complications related to BTI are reported only as isolated cases (fatal arrhythmia, gastroparesis and mediastinitis), probably due to technical difficulties during procedures[16]. In an initial study, Pasricha *et al*[17] reported 82% of patients with dysphagia improvement after BTI. Annese *et al*[18] showed 75% of subjects with dysphagia

remission at 2 years follow-up; however some of the patients required at least one repeated BTI. The short-term effectiveness of BTI was also investigated by Neubrand *et al*[19] using esophageal manometry 1 wk after treatment; LES pressure dropped from 62.1 ± 15.2 mmHg to 43.1 ± 12.5 mmHg ($P < 0.01$). However, symptomatic remission induced by BTI usually decreases within one year (40.6% at one year or longer)[20]. Also, the appearance of antibodies against botulinum toxin or development of regional fibrosis can dissipate the effects of successive injections[21]. BTI was found to be effective only in the short-term evaluation, with reduced benefit within 2 years after injection and eventually with none after repeated injections[22,23]. Because of these limitations, BTI is best reserved for patients who are too ill to undergo surgery, such as elderly patients or patients whose disease is complicated by overlapping diseases or those declining surgery or PD[24]. Compared to PD and surgery (myotomy), BTI was clearly inferior at mid and long term efficacy[25]. A recent Cochrane Review evaluated 178 patients from 6 randomized, controlled trials after esophageal dilation *vs* endoscopic botulinum toxin injection. At one year follow up, up to 74% of patients who underwent BTI were found to have failed treatment, compared to 30% of patients who underwent dilation[26]. Also, Campos *et al*[20], performing a systematic review and a meta-analysis on 7855 achalasia patients, found a better symptomatic relief when treated by PD than BTI. A recent review on 5 best evidence papers trials on BTI *vs* surgical myotomy reported that surgery should be the first line treatment due to its superior long-term clinical success rate[27]. BTI has been used as rescue treatment after unsuccessful PD or surgical myotomy[28]. There is an increased risk for perforation during PD[29], or increased difficulty of performing esophagomyotomy after BTI[30].

PNEUMATIC DILATION

Pneumatic dilation (PD) in patients with achalasia aims to forcibly fracture the muscularis propria, decreasing LES pressure and thereby improving bolus transit through cardia. Forceful dilation of the LES dates back to 1674, when Willis used whalebone as a prototypic bougie to accomplish distraction of the muscular fibres in the esophago-gastric junction[31]. Subsequently, dilation has been performed by various techniques. In fact, up to date, there is no well-standardized, unique technique performing PD in achalasia patients, with different technical modifications. Recently, a ⩾ 3 cm polyethylene low-compliance balloon (Rigiflex Achalasia Balloon Dilator, Boston Scientific, Boston, MA, United States) has been most widely used because it is considered the safest and most effective[20], nevertheless other companies produce analogous devices. These polyethylene balloons are more consistent than latex ones, with the advantage that a fixed diameter (usually as 30, 35, 40 mm sizes) can be achieved during inflation. The position

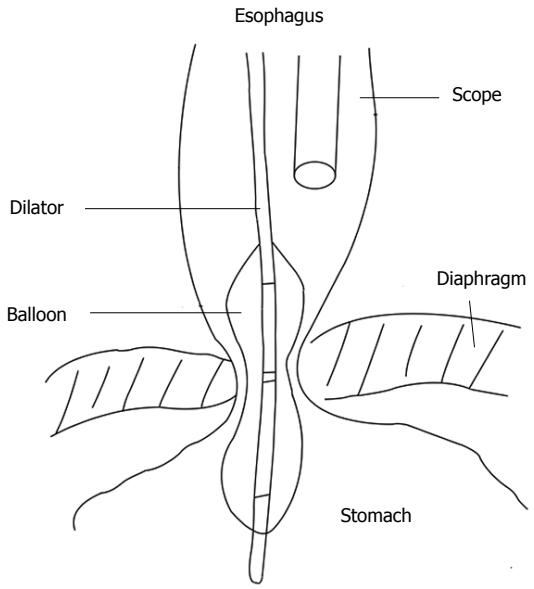

Figure 1 Pneumatic dilation under direct endoscopic guidance (from ref.[32]).

of balloon across the LES is typically performed using a guidewire and fluoroscopy. In recent times, PD has been performed during endoscopic direct imaging rather than fluoroscopy guidance in order to avoid radiation exposure and to obtain a better clinical response and limiting complications (Figure 1). However, even if both fluoroscopically and endoscopically guided PD are safe and effective techniques, the authors were not able to demonstrate differences in outcomes[32]. During endoscopy, a metallic guidewire with a soft distal tip is passed through the LES, then the balloon is put along the wire, until its centre is correctly placed through the esophagogastric junction. After fixing the device by a firm grasp to avoid distal migration during the procedure, the balloon is filled slowly with air until a value of 7 to 10 psi on sphygmomanometry is reached. The aim is to sustain dilation until the LES waist appears closed around the balloon; some prefer a prolonged dilation whereas others deflate the balloon immediately afterwards[33]. Then the balloon device and guidewire are removed. Commonly, blood presence around the balloon cannot be considered a useful marker of successful PD. With the use of a Rigiflex Achalasia Balloon Dilator, the mean time required to reach the required pressure for PD was reported to be 73 s (range, 6-240 s), with a mean dilation pressure of 10.9 psi (range, 7-18)[20]. Usually, an esophageal RX transit with hydro-soluble (gastrografin) contrast agent can be carried out after anesthesia recovery, to verify the presence of lumen perforation and perhaps treatment outcome. There is general agreement that a single dilation, when successful, could be more efficient over time. However, patients typically require serial dilations to remain clinically silent. Success rates of PD are reported up to 84.8% within one month after the procedure, as stated in a systematic review carried out by

Campos *et al*[20] However, success rates declined on longitudinal follow-up; in fact, the success rate was reported to be 73.8% at 6 mo, 68.2% at one year, and 58.4% at 3 years or longer. Also, 25% of patients required a second or a repeated PD. Several studies with a long-term follow-up are currently available. Eckardt *et al*[34] showed with a unique PD a response of 40% at 5-year follow-up, and patients with relieved symptoms at 5 years were more likely to continue in this way, whereas Zerbib *et al*[35] reported an estimated efficacy of 97% and 93% at 5 and 10 years respectively, but frequently with repeated PD. In a study on 209 patients with a mean follow up of 70 mo, a success rate with balloon dilation was observed in 72% of subjects[36]. However, in these studies PD is not routinely repeated, but only performed on demand for still-symptomatic patients; instead, in the study by Hulselmans *et al*[36] patients repeated PD with a bigger balloon only if manometry and barium esophagram did not show optimal treatment outcomes. Long-term efficacy of PD was investigated only in a few studies that have followed-up patients over a decade[37]. The authors concluded that PD, when performed by experienced operators, can achieve good to excellent outcomes (defined as a better swallowing ability and a better quality of life); however, only a few patients can be definitively treated with a first, single dilation, needing repeated dilations at long term follow-up[38]. The most common complication of PD is esophageal perforation, being reported to occur, fortunately, in less than 5% of dilations. Moreover, improvements in balloon materials and other factors have decreased the incidence of perforation to 1.6% on average[20,39]. PD-associated perforation seems to not be related to any well confirmed risk factors and there is no evidence that larger balloons are linked to an increased perforation rate[40]. The PD-linked overall complication rate is estimated to be lower than 10%; these include perforation, transient non-cardiac chest pain, esophagogastric lacerations, hematomas, hemorrhage, fever, and formation of diverticula[41]. Esophageal perforation may be treated with a completion myotomy emergently by a laparotomy, or more recently, performed *via* laparoscopy[42]. Reflux symptoms can be present after PD, reflecting a success in widening the gastroesophageal junction[43]. Several factors are considered responsible for predicting outcomes after PD. Eckardt *et al*[44] showed that, if after PD a manometrical-determined LES pressure of 10 mmHg or less is achieved, this can be the most important predictor of long-term clinical response and that response rates in patients younger than 40 years are relatively lower. Duranceau *et al*[45] reported that grade 4 achalasia patients ("sigmoid esophagus" or "end-stage" disease) generally do not show a good response to PD (or to other treatments). Ghoshal and colleagues instead reported that poor outcomes were associated with sex (male gender) and with a missed drop in LES resting-pressure > 50% after dilation, but they were not related to age, or other factors such as elevated dysphagia score, presence of regurgitation, end stage esophagus, or initial LES resting-pressure[46,47]. Recent use of HRM has suggested, based on Chicago classification, that those with type I and type II (classic and compressive achalasia, respectively) respond much better to PD than those with type III (spastic achalasia)[48]. The role of PD in comparison to surgery is still debated. Both techniques produce an optimal initial resolution of dysphagia; nevertheless surgery is considered to be superior at longer follow up[22,49]. A study by Gockel *et al*[50] showed comparable clinical outcomes with surgical myotomy and PD, but surgery achieved a better LES resting-pressure drop. On the other hand, only a few prospective randomized controlled trials comparing these techniques are available in the literature. There has been a single randomized prospective trial examining outcomes in 81 patients after Heller myotomy plus Dor fundoplication *vs* pneumatic dilation, with a median follow-up of about 5 years[51]. In this trial, investigators found that patients undergoing myotomy resulted in similar relief of dysphagia, but had fewer relapse of symptoms at longer follow-up than those patients undergoing PD (95% success rate *vs* 65%, respectively). However, an important limitation of this study was that dilation was performed with a Mosher bag rather than with a Rigiflex balloon dilator, currently considered the most effective dilator. In a prospective randomized study by Boeckxstaens *et al*[52], PD was compared with surgical therapy (laparoscopic Heller myotomy plus Dor' s fundoplication), using a rigorous design. The study included 201 patients, with a 43 mo mean follow-up; at 12 mo, the two groups showed no significant difference in dysphagia and overall Eckardt score. At 24 mo, the success rate was similar; there was no difference in LES resting-pressure, esophageal transit during RX-barium swallow, or quality of life. However, when a 35-mm balloon was used for dilation in this study, perforation occurred in 4 (31%) of 13 patients. This protocol was abolished during the study. With a balloon 30 mm in diameter, the perforation rate decreased to 4%. In either case, however, PD is associated with a substantial risk of perforation and has not been shown to be clearly superior to surgical therapy in terms of safety. PD can be also considered for a second treatment ("salvage") in patients that had a prior unsuccessful myotomy, but the efficacy rate is reported to be lower when compared to those patients who underwent only dilation[53].

PER ORAL ENDOSCOPIC MYOTOMY

Per oral endoscopic myotomy (POEM), first described by Inoue *et al*[54,55] developed from a technique to access the mediastinum in Natural Orifice Transluminal Endoscopic Surgery (NOTES)[56]. The technique of POEM can be summarized in the following steps: (1) lift of submucosa by injection, and creation of esophageal mucosa tear; (2) tunnellization in the submucosal

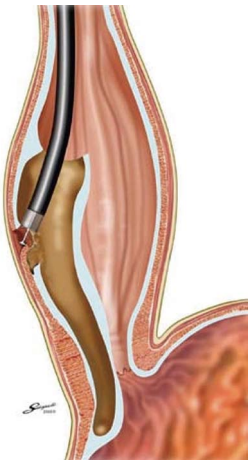

Figure 2 Per Oral Endoscopic Myotomy; creation of submucosal tunnel and inner myotomy (from ref. [55]).

space; (3) identification and separation of esophageal circular muscle; (4) myotomy; and (5) repair of the mucosal tear. A fundamental step of POEM is the creation of a submucosal tunnel with subsequent closure of the mucosal tear entry site away from the myotomy (Figure 2). An endoscopic myotomy of inner circular muscle within this tunnel is then performed, accomplishing a minimal dissection of the LES circular muscle. The myotomy of clasp fibers is performed by grasping the inner muscle layer with a hook and dividing them with an electrocautery-based device. This dissection of muscle is continued distally until it is extended 1-2 cm into the cardia. The overall cut length is approximately 12 cm. The mucosal defect is closed with endoscopic clips. Finally, an easy and smooth passage of an endoscope through the gastroesophageal junction is confirmed at the end of the procedure. This procedure is performed during general anaesthesia with endotracheal intubation. Inoue *et al*[55] initially indicated POEM for the treatment of early-stage achalasia, but recently he described POEM performed in 16 sigmoid achalasia patients, extending the indication to all categories of achalasia, including longstanding disease. Contraindications to endoscopic myotomy include severe pulmonary disease, significant coagulation disorder and prior therapy that compromise esophageal mucosal integrity. Inoue *et al*[57] have treated 43 cases of achalasia, with a maximum follow-up period of 1 year 9 mo. Symptoms of achalasia decreased or disappeared in all patients. The LES pressure decreased significantly after the procedure. No specific complications related to POEM were reported. Although about 10% of patients had gastroesophageal reflux disease after the procedure, symptoms resolved in response to treatment with a proton-pump inhibitor. Actually, there are only series from a few centers[58,59] but literature on POEM is drastically increasing, reflecting the world wide interest in this technique. In follow-up studies, von Renteln *et al*[60] used POEM to treat 16 patients with achalasia and reported similar, favourable results; Li *et al*[61] reported a treatment success (Eckardt score $\leqslant$ 3) in 96% (95 of 99) of patients treated with a full-thickness myotomy and in 95% (115 of 121) of patients treated with circular muscle myotomy. Recently, 70 patients who underwent POEM at 5 centres in Europe and North America, were enrolled in a prospective, international, multicenter study, aiming to determine the outcomes of this technique[62]. At the first follow-up (3 mo) after the procedure, 97% of subjects displayed complete symptom relief (95%CI: 89%-99%); dysphagia and other mean symptoms scores dropped from 7 to 1 ($P < 0.001$) and LES resting-pressures fell from 28 to 9 mmHg ($P < 0.001$). At 6 and 12 mo follow-up visits, symptom relief was found in 89% and 82% of patients, respectively. The authors concluded that POEM, at a 10 mo mean follow-up, can be considered an effective treatment in the management of achalasia. Swanstrom *et al*[63] described 6-mo physiological and symptomatic outcomes in 18 patients after POEM for achalasia. The authors found that all investigated patients displayed remission of dysphagia (dysphagia score $\leqslant$ 1), whereas only 2 patients showed Eckardt scores > 1, related to persistent non cardiac chest pain. During the POEM procedure, 3 intraoperative complications were noted: 2 gastric mucosal tears and 1 esophageal perforation. In all patients, surgeons were able to repair the esophageal and gastric wall endoscopically without any further comorbidity. All patients reported a persisting dysphagia resolution at 11.4 mo mean follow-up. Postoperative LES relaxations and esophageal transit were found to be strongly improved, when investigated by manometry and RX barium esophagogram, respectively. However, the postoperative presence of gastroesophageal reflux was objectivized in 46% of patients. The latter data are in contrast with the low rate (10%) of reflux reported by Inoue[55]. In theory, POEM might not damage anti-reflux barriers such as phrenoesophageal ligamentous attachments and, therefore, may not additionally require an anti-reflux procedure. Gastroesophageal reflux should be prevented to some extent, but objective studies, as previously performed after laparoscopic Heller myotomy plus fundoplication[64,65] are needed. Recently, Verlaan *et al*[66] studied the physiological outcomes of POEM on the esophagogastric junction, reporting 60% rate of reflux esophagitis at endoscopy. Although POEM is expected to become a state-of-the-art technique for minimally invasive surgery in patients with achalasia, it is associated with the risk of serious complications such as mediastinitis and peritonitis caused by perforation of the esophagus or stomach. At present, therefore, it should be performed with caution and only by operators proficient in both esophagoscopic submucosal dissection and open or laparoscopic Heller myotomy. Recent studies compared POEM with laparoscopic Heller myotomy alone[67], or with laparoscopic Heller myotomy plus a partial fundoplication[68], showing similar rates in dysphagia relief. Wider use of POEM would require the results of large,

multicentre clinical trials demonstrating the safety of this procedure. Follow-up studies should also be performed to establish the long-term effectiveness of POEM.

CONCLUSION

As endoscopic treatment for achalasia, PD is superior to BTI. Botulinum toxin injection may be reserved for severly ill patients. It is difficult to make definitive conclusions regarding the comparison between PD and surgery with fundoplication, however Heller mytomy with fundoplication appears to be better especially in young patients. POEM is expected to become a valid substitute for Heller myotomy, but long-term outcomes, the real incidence of "*de novo*" GERD and safety must be confirmed.

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MINIREVIEWS

Laparoscopy for ventriculoperitoneal shunt implantation and revision surgery

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Abstract

Ventriculoperitoneal shunting (VPS) is a widely accepted technique for the treatment of hydrocephalus. The probability of shunt dysfunction is pretty high throughout life. Laparoscopy has become a valuable tool to perform VPS and treat abdominal complications. An electronic literature search was performed to reveal the published data relating laparoscopy and ventriculoperitoneal shunt in Medline, Embase, Scielo and Lilacs databases. The keywords employed were "laparoscopy" OR "laparoscopic surgery" AND "ventriculoperitoneal shunt" OR "shunt" AND "surgery" OR "implantation" OR "revision" OR "complication". No high quality trials were developed comparing conventional laparotomic incision *vs* laparoscopic approach. Both approaches have evolved and currently there are less invasive options for laparotomy, like periumbilical small incisions; and for laparoscopy, like smaller and less incisions. Operating room time, blood loss and hospital stay may be potentially smaller in laparoscopic surgery and complications are probably the same as laparotomy. In revision surgery for abdominal complications after VPS, visualization of whole abdominal cavity is fundamental to address properly the problem and laparoscopic approach is valuable once it is safe, fast and much less invasive than laparotomy. Ventriculoperitoneal shunting is a widely accepted technique for the treatment of hydrocephalus. Laparoscopy assisted shunt surgery in selected cases might be a less invasive and more effective option for intrabdominal manipulation. The laparoscopic approach allows a better catheter positioning, lysis of fibrotic bundles and peritoneal inspection as well, without any additional complication.

Key words: Cerebrospinal fluid shunt; Hydrocephalys; Laparoscopy

Core tip: Review of application of laparoscopy in ventriculoperitoneal surgery.

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INTRODUCTION

Shunt surgery represents a paramount procedure in neurosurgical practice, as the most widely performed central nervous system surgery. The preferred modality is the ventriculoperitoneal shunt (VPS), which connects the lateral ventricles and the peritoneal cavity[1-4].

Up to 80% of shunts implanted for treatment of hydrocephalus may fail at some point during the patient's life, with approximately 30% failing within the first year. Although shunt placement is a common procedure and is considered safe, several complications may occur. Shunt-

related complications, such as obstruction, overdrainage, loculation, and infection, sometimes require challenging surgical approaches associated with increased morbidity[1-6].

Abdominal complications of VPS are not rare, and the common mechanism involves epithelial responses to the presence of the catheter, which cause peritoneal retraction, intra-abdominal cerebrospinal fluid (CSF) collections, and adhesions. These complications usually worsen with multiple peritoneal revisions, sometimes resulting in peritoneal sclerosis that make further shunt implantation infeasible[7].

Within this context, the laparoscopic approach has grown in popularity as an alternative method for shunt implantation and especially for revision surgery after abdominal complications. This paper summarizes current concepts about its application.

RESEARCH

A critical review of the literature was performed after searching the MEDLINE, Embase, SciELO, and LILACS databases for published data on laparoscopy and ventriculoperitoneal shunting. The search query employed was "laparoscopy" OR "laparoscopic surgery" AND "ventriculoperitoneal shunt" OR "shunt" AND "surgery" OR "implantation" OR "revision" OR "complication".

We selected all papers in english, spanish and portuguese. The above search strategy yielded 240 manuscripts. Of these, 110 discussed other uses of laparoscopy not related to ventriculoperitoneal shunting, such as laparoscopy for abdominal and urological surgery. One hundred and thirty papers addressed the topic of interest. As some of these articles presented outdated data or very similar discussions, we selected 30 up-to-date manuscripts discussing different points of view to summarize recent, pertinent information about applications of laparoscopic surgery in ventriculoperitoneal shunting (Figure 1).

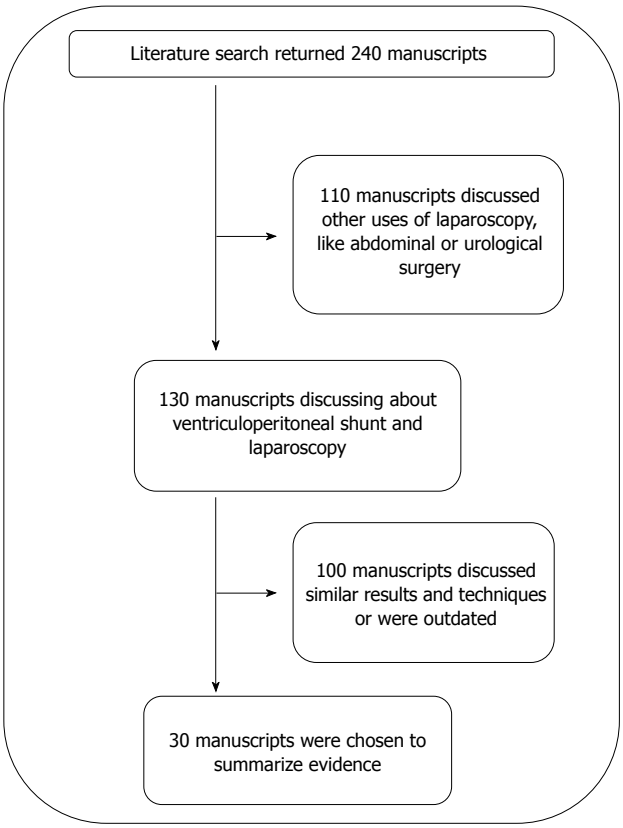

Figure 1 Flowchart of articles evaluated in revision.

LAPAROSCOPY FOR SHUNT IMPLANTATION

Several reports highlight the utility of the laparoscopic approach for abdominal shunt insertion through less invasive incisions[8-10]. No high-quality trials were found comparing conventional laparotomy *vs* laparoscopic approaches. The rationale supporting conventional laparotomy includes factors such as the simple learning curve, as it can be performed by neurosurgeons, and its established success rate. The rationale for laparoscopic approaches includes wide view of catheter implantation, ability to choose the best site for fixation, and confirmation of patency[11-15].

Both approaches have evolved. Currently, less invasive options are available both for laparotomy - such as small periumbilical incisions - and for laparoscopy, such as smaller and fewer incisions using 2-mm trocars[16-20].

Operating room time, blood loss, and hospital stay may be reduced in laparoscopic surgery, and complications are probably the same as with laparotomy[19].

LAPAROSCOPY FOR REVISION SURGERY

In revision surgery for abdominal complications after VPS, the main findings may be abdominal adhesions, peritoneal thickening and retraction, and CSF pseudocysts. Additionally, after complicated VPS, catheter malfunctioning may occur due to migration, occlusion, and presence of foreign bodies[8,21-23].

In such scenarios, visualization of the whole abdominal cavity is essential to addressing the issue properly. The laparoscopic approach is valuable in this setting because it is safe, fast, and much less invasive than laparotomy, and is thus associated with fewer complications[24-27].

DISCUSSION

Ventriculoperitoneal shunting is a widely accepted technique for the treatment of hydrocephalus. The standard procedure to insert the peritoneal catheter requires an abdominal incision, muscle dissection, and opening of the peritoneum. The probability of lifetime shunt dysfunction is quite high. Abdominal complications are major causes of dysfunction. The peritoneal space is forced to accommodate a foreign body (catheter) and receive the flow of approximately 21 mL of CSF per hour, resulting in epithelial responses which may lead to inflammation

and obstruction[1-4].

Several alternative procedures have been reported as temporary or permanent solutions to VPS failure, such as catheter implantation in other distal sites in the cervical, thoracic, and abdominal regions. The ventriculo-omental bursa shunt, with catheter insertion through the foramen of Winslow, has been described, even in cases of peritonitis or peritoneum adhesion. However, all of these options are considered third-line procedures, due to their higher complexity and high complication rates[27].

Laparoscopic-assisted surgery has become an useful option, as it allows abdominal exploration with shorter surgical time and complications. In 1993, Armbruster *et al*[10] and Basauri *et al*[11] described the laparoscopically assisted implantation of ventriculoperitoneal shunts, and in 1995, Kim first described the laparoscopic management of an abdominal complication[11,21].

On the other hand, laparoscopic surgery for other purposes may interfere with VPS function and even cause obstruction. The impaction of soft tissue or air within the distal catheter as a consequence of peritoneal insufflation may cause shunt obstruction[28]. Furthermore, increased abdominal pressure may have a negative effect on intracranial pressure (ICP). Human data on the effects of laparoscopy on ICP are lacking, but ICP increases significantly with abdominal insufflation and correlates with laparoscopic insufflation pressure. Thus, laparoscopy should be performed cautiously in patients with elevated baseline ICP[29].

In conclusion, we believe that laparoscopic-assisted shunt surgery in selected cases might be a less invasive and more effective option for intra-abdominal manipulation. The laparoscopic approach also enables better catheter positioning, lysis of fibrotic bundles, and peritoneal inspection without any additional complications.

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ORIGINAL ARTICLE

Updates on gastric electrical stimulation to treat obesity: Systematic review and future perspectives

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Abstract

AIM: To evaluate the current state-of-the-art of gastric electrical stimulation to treat obesity.

METHODS: Systematic reviews of all studies have been conducted to evaluate the effect of different types of gastric electrical stimulation (GES) on obesity.

RESULTS: Thirty-one studies consisting of a total of 33 different trials were included in the systematic review for data analysis. Weight loss was achieved in most studies, especially during the first 12 mo, but only very few studies had a follow-up period longer than 1 year. Among those that had a longer follow-up period, many were from the Transcend® (Implantable Gastric Stimulation) device group and maintained significant weight loss. Other significant results included changes in appetite/satiety, gastric emptying rate, blood pressure and neurohormone levels or biochemical markers such as ghrelin or HbA1c respectively.

CONCLUSION: GES holds great promises to be an effective obesity treatment. However, stronger evidence is required through more studies with a standardized way of carrying out trials and reporting outcomes, to determine the long-term effect of GES on obesity.

Key words: Gastric electrical stimulation; TANTALUS® system; Transcend® implantable gastric stimulator; Retrograde gastric electrical stimulation; Gastric vagal nerve stimulation; Gastric pacing; EMPOWER trial; Dual-lead implantable gastric electrical stimulation trial; Laparoscopic obesity stimulation survey; Screened health assessment and pacer evaluation

Core tip: Obesity is a major issue in many countries. Current medical treatments do not last long enough and while surgical interventions are more effective, they imply a higher risk of complications. This review contains the most up-to-date information on gastric electrical stimulation, which has shown to be a less invasive and potentially effective treatment option for the treatment of obesity.

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INTRODUCTION

The rate of excess weight and obesity has constantly increased over the past 30 years, and about one third of the world's adult population is overweight[1]. Impressive

excess weight and obesity rates have also been recorded in children and adolescents[2,3]. In Northern America, two thirds of the population is either overweight or obese and in most European countries, the prevalence ranges from 40% to 50%[4]. Projections up to year 2030 indicate that more than 36% of the population in developed countries will be overweight and that more than 22% will be obese[5].

Obesity is a complex multi-factorial, psychoneuroendocrine and metabolic problem, and not simply an imbalance between energy intake and energy expenditure. Obesity is associated with many co-morbidities, including diabetes, hypertension, dyslipidemia, obstructive sleep apnea, weight-related arthropathies, and urinary incontinence[6]. Recent studies also showed that obesity is a major risk factor for cancer[6,7]. Obesity and its co-morbidities lead to an increased use of the health care system and this consequently has a negative economic outcome[8]. Up to 20% of total annual United States healthcare expenditures, around 190 billion dollars, may have been spent on obesity-related medical care in 2005[9,10].

The main therapeutic approaches to obesity are lifestyle correction, pharmacotherapy, surgery and electrical devices[11].

Lifestyle management includes diet and exercise, aiming for more energy expenditure as compared to food intake. However, weight loss maintenance by means of dieting is difficult to manage in the long term. Similarly, Food and Drug Administration (FDA)-approved weight control drugs, such as sibutramine and orlistat, have a very low success rate, and may have considerable side-effects[12].

Surgery seems to be the only effective treatment to achieve sustainable weight loss[13,14] and reversal of obesity-related co-morbidities. Surgical treatment includes three subgroups-restrictive, malabsorptive, and combined restrictive and malabsorptive procedures. Bariatric surgical options can result in up to 80% of long-term excess weight loss (EWL)[15]. However, surgical interventions are invasive and this entails potential postoperative complications[16-19]. Additionally, a very small percentage (less than 1%) of eligible obese patients eventually undergo bariatric surgery[20,21]. This seems to be related to various reasons, including lack of insurance coverage in some countries, as well as psychological factors related to the permanent anatomical changes and potential postoperative complications[20,21].

Less invasive anti-obesity therapies, which are increasingly used, include intragastric balloons (space-occupying devices) and bezoars, which are collections that accumulate, coalesce and are retained in the gastrointestinal tract[22]. These devices are not very well tolerated and long-term results are disappointing. More recently, endoluminal bypassing devices, such as the Endobarrier® or the duodenojejunal bypass liner, seem to be effective in improving glycemia in type 2 diabetes patients by improving insulin sensitivity, demonstrating a crucial role of the duodenum in the genesis of the metabolic syndrome. However, these devices must be anchored endoscopically at the pylorus or at the esophagus with full-thickness fixations, and their presence is often symptomatic, with spastic pain.

The gastric electrical stimulator (GES) has been identified as a potential alternative minimally invasive surgery, based on the growing knowledge on gastrointestinal physiology[23].

The concept of GES to treat obesity was initially proposed in 1995 by Cigaina[15,24,25] who demonstrated the proof of the concept in a series of animal experiments. The exact mechanisms of GES remains largely unknown, but it is thought to impair physiological gastric electrical activity (*i.e.*, slow waves), inducing gastric distension, gastric accommodation reduction, and stomach peristalsis inhibition, leading to delayed gastric emptying and increased satiety[26]. The type of stimulation can be divided into two groups-antegrade and retrograde. The difference between them is the direction of conduction. Antegrade stimulation imposes forward conduction of impulses whereas retrograde stimulation conveys impulses in a backward fashion. GES is also thought to have an effect on neuronal activity in the brain and to affect satiety hormones[26].

Since the discovery of GES, many animal experimental studies have been performed, followed by several clinical trials on human subjects. However, the number of high quality trials is limited and no meta-analysis on GES exists to date. In this systematic review of the literature, we aimed to provide the most up-to-date state-of-the-art on the clinical applications of GES stimulators for obesity.

MATERIALS AND METHODS

The methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[27].

Literature search

A broad search was initially performed using the key words "Gastric Electrical Stimulation" and "Obesity" in MEDLINE®/PubMed® and in The Cochrane Library. A more specific search was then performed using the name of each device, as outlined in Table 1. No limit was set at this stage. Duplicate articles were removed and further relevant articles were identified by cross-referencing all searched articles.

Study selection

All published studies investigating the effect of various types of GES on obesity were included. Either an abstract or a full text of each study was manually assessed based on the following exclusion criteria: (1) Language of the article is not English; (2) GES was used for diseases other than obesity (*e.g.*, gastroparesis); (3) Non-gastric stimulation (*i.e.*, stimulation in other areas such as intestine); (4) Animal or experimental study; (5) Primary outcome is not clinical (*i.e.*, no weight, BMI or appetite change measured); and (6) Abstracts without adequate

Table 1 Search terms and results obtained from different databases

Search terms	Database 1 Pubmed	Overlapping Pubmed articles	Total number of articles from Pubmed	Database 2 Cochrane	Database 3 Medline
Gastric electrical stimulation and obesity	145	0	145	5[1]	9[1]
TANTALUS® and obesity	12	7	5	1[1]	6[1]
Enterra® and obesity	6	6	0	0[1]	2[1]
Transcend® and obesity	13	5	8	0[1]	4[1]
Implantable gastric stimulator and obesity	22	12	10	3[1]	2[1]
Retrograde gastric electrical stimulation and obesity	13	3	10	0[1]	2[1]
Gastric pacing and obesity	26	20	6	1[1]	8[1]
Neural gastric electrical stimulation and obesity	6	6	0	0[1]	3[1]
Total number of articles after duplicate removal			184		

[1]Duplicate articles (*i.e.*, these articles are already included in the results of the Pubmed literature search).

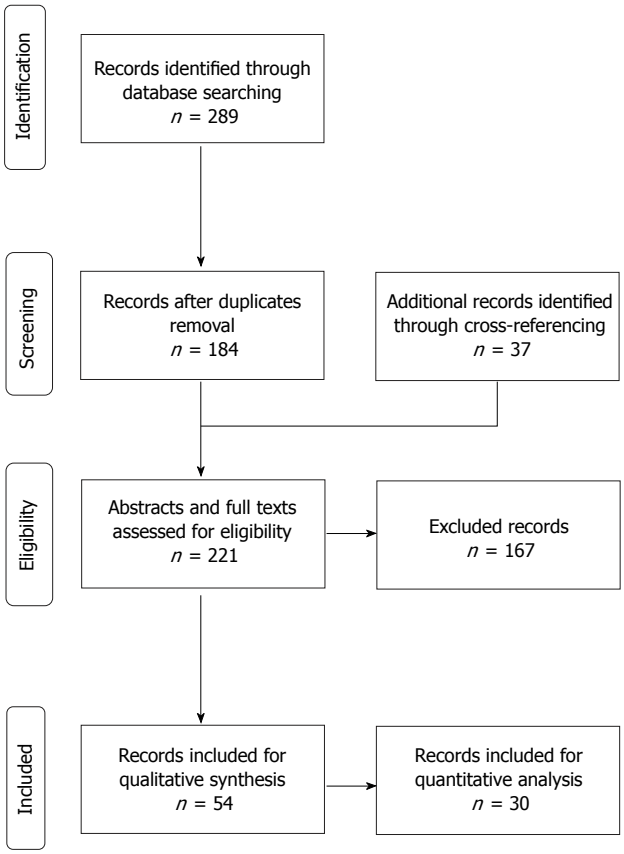

Figure 1 Preferred reporting items for systematic reviews and meta-analysis flow chart.

amount of information on quantitative data. From the studies that remained after the exclusion process, only clinical trials on human subjects were included for data extraction and analysis.

Data extraction

Data were extracted and entered into a pre-designed Excel spreadsheet. The areas of interest were the following: (1) Study designs-sample size, drop-out rate, follow-up period, mean age of participants, baseline weight, BMI, dietary/lifestyle information; (2) GES device parameters-device and electrode implantation sites, type of stimulation, pulse width, amplitude, frequency; and monitoring during and after implantation including any complications due to implantation; (3) Significant outcomes-weight loss, appetite reduction, increased satiety, HbA1c, ghrelin level and gastric emptying rate; and (4) Adverse effects, side-effects or complications at follow-up consultations.

RESULTS

Study selection

The literature database search yielded 289 records, including duplicates. After removing duplicate records (n = 105), 184 articles were collected from various combinations of search terms and databases outlined in Table 1. These records were screened manually to identify further relevant articles and as a result, 37 additional studies were added by cross-referencing. Out of a pool of 221 abstracts and full-text articles, 167 articles were excluded. In a total of 54 articles, 30 clinical trials on human subjects were identified and were included for data extraction. The other 24 studies including reviews, reports, and editorials were excluded from the data analysis but were used for qualitative synthesis, as reported in Figure 1.

General study characteristics

The summaries of all included studies are provided in Tables 2-6. Most studies were non-randomized trials, except 4 studies (including 2 SHAPE trials and 1 U.S. O-01 trial) that were randomized trials. Four Transcend® studies[21,28-30] conducted Baroscreen™ screening, and five Transcend® studies[21,28,31-33] required participants to follow a certain diet and change in behavior. None of the studies assessing other devices required diet or lifestyle changes with the exception of the EMPOWER study[34] for vagal nerve stimulation.

Sample size for most studies was very small. Out of 31 different trials, 24 had about 30 or fewer participants. Five Transcend® studies[20,21,30,35,36] had large participant numbers, but most of them had a drop-out rate of more than 50% by the end of their trials. The studies with low drop-out numbers were the SHAPE trial by Shikora *et al*[21], 2009 (10 drop-outs), and the two TANTALUS® trials[37,38] (0 drop-out in both trials). The EMPOWER study by Sarr *et al*[34] in 2012 had 41 drop-outs but had a large population group of 294 at the beginning of the study,

Table 2 Summary of TANTALUS® trials

Ref.[1]	Sample size (*n*), enrolled/completed	Mean age (yr)	Mean weight, (kg)/ mean BMI (kg/m^2)	Follow-up (mo)	Lifestyle change (required/ advice given)	Co-morbidities
Lebovitz *et al*[38], 2013	40/40	NR	110.5 ± 3.5/NR	NR	NR/NR	NR
Sanmiguel *et al*[70], 2009	14/11	42	107.3 ± 20.1/39 ± 1	6	N/Y	T2DM
Bohdjalian *et al*[39], 2009	24/21	50.0 ± 1.6	123.7 ± 4.5/41.9 ± 1.0	12	NR/NR	T2DM
Policker *et al*[37], 2009	50/50	NR	NR/NR	6+	NR/NR	T2DM
Bohdjalian *et al*[71], 2009	13/13	53.8 ± 2.6	104.4 ± 4.4/37.2 ± 1.1	3	N/Y	T2DM
Policker *et al*[69], 2008	12/12	50.8 ± 2.2	130 ± 6.5/NR	9	N/Y	T2DM
Sanmiguel *et al*[43], 2007	12/11	39.1 ± 8.9	NR/41.6 ± 3.4	1.5	N/NR	T2DM
Bohdjalian *et al*[72], 2006	12/9	36.1 ± 2.8	128.8 ± 5.2/43.2 ± 2.7	12	N/Y	HTN

[1]All trials were open-label and none were randomized. T2DM: Type 2 diabetes.

Table 3 Implantable gastric stimulator Transcend®: Studies summary

Ref.	Type of research	Sample size, (enrolled/completed)	Mean age (yr)	Mean weight, (kg)/ mean BMI (kg/m^2)	Follow-up (mo)	Lifestyle change (required/advice given)	Baroscreen®
Korner *et al*[28], 2011	Randomized + D, PC (SHAPE)	13/13	48.8	113.1/40.6	24	Y/Y	Y
Shikora *et al*[21], 2009	Randomized + P, D, M, PC (SHAPE)	190/180	43.9	NR/41	12	Y/Y	Y
Hoeller *et al*[73], 2006	Non-randomized	8/7	48.1	112.5/41.3	23	NR/NR	N
Champion *et al*[29], 2006	Non-randomized + O	24/21	43	92/33	6	Y/Y	Y
Miller *et al*[30], 2006	Non-randomized + P, M (LOSS trial)	91/25	41	116/41	24	N/Y	Y
Shikora *et al*[20], 2005	randomized + D, PC (O-01 trial)	103/34	40	129/46	29	NR/NR	N
Shikora *et al*[20], 2005	Non- randomized + O, M (DIGEST)	30/23	39	NR/42	24	Y/Y	N[1]
Cigaina *et al*[32], 2004	Non- randomized	65/NR	39.4 ± 3.4	132.7 ± 27.3/46.9 ± 7.07	96[2]	Y/Y	NR[1]
Favretti *et al*[74], 2004	Non- randomized	20/20	40	115/40.9	10	N/Y	NR
De Luca *et al*[36], 2004	Non- randomized + P (LOSS trial)	69/20	41	115/41	15	NR/NR	NR
Cigaina *et al*[75], 2003	Non- randomized	11/11	39.4 ± 3.4	121.7 ± 5.1/46.0 ± 2.5	8	N/Y	NR
McCallum *et al*[35], 2002	randomized + D	103/NR	40	NR/46	12	NR/NR	NR
D'Argent *et al*[76], 2002	Non- randomized + P, O	12/NR	40.6	122.2/42.7	9	NR/NR	NR

[1]No Baroscreen® conducted but binge eating assessment questionnaire and a psychological evaluation were carried out; [2]This study had four different cohorts over the 8-yr period, from 1996 to 2004.

Table 4 Retrograde gastric electrical stimulation-studies summary

Ref.[1]	Sample size (enrolled/ completed)	Mean age (yr)	Mean weight, (kg)/mean BMI (kg/m^2)
Zhang *et al*[41], 2013	16/16	39	NR/32.1
Yao *et al*[44], 2005	12/12	29.4 ± 8.6	62.62 ± 8.29/23.2 ± 2.6
Yao *et al*[77], 2005	12/12	29.4 ± 8.6	62.62 ± 8.29/23.18 ± 2.62

[1]All trials were non-randomized; no follow-up length and lifestyle change advice reported.

making it one of the most powerful studies for vagal stimulator and obesity.

There were two articles about the Transcend® Implantable Gastric Stimulator (IGS) (MEDTRONICS, Inc., Minneapolis, MN, United States) based on the same data, but because each article had two different trials, the total number of trials did not change. There was one article from the gastric pacing device group, which included 3 different cohorts at different time periods[33]. As a result, it was counted as 3 different trials.

The full text for one article, "The implantable gastric stimulator for obesity" by Miller *et al*[30] was not obtained, but relevant data from this study was inferred from a 2006 review article. The majority of the studies did not report stimulation parameters (Table 7). Most common forms of pulses reported were "Train of short pulses".

In all studies, the generator was externalized and in most cases they were implanted in subcutaneous layers of the anterior abdominal wall. The electrodes connected to the generator were implanted in different locations of the stomach, depending on the type of GES. TANTALUS® had electrodes in the fundus and antrum. Transcend and RGES had them in the lesser curvature of the anterior medial wall and in the greater curvature of the distal antrum respectively. Gastric pacing had electrodes in either

Table 5 Vagal nerve electrical stimulation studies summary

Ref.	Type of research	Sample size (enrolled/completed)	Mean age (yr)	Mean weight, (kg)/ mean BMI (kg/m^2)	Follow-up (mo)	Lifestyle change (required/advice given)	Co-morbidities
Sarr *et al*[34], 2012 [EMPOWER study]	Randomized, Prospective Double blind, Multicentre	294/253	46	NR/41	12	Y/Y	T2DM HTN
Camilleri *et al*[78], 2009	Prospective[1], Multicentre, O	27/25	40.1 ± 1.8	NR/39.3 ± 0.8	6	NR/NR	N
Camilleri *et al*[79], 2008	Prospective, Multicentre, O	31/NR	41.4 ± 1.4	NR/41.2 ± 0.7	6	NR/NR	T2DM

[1]There were two phases in this study. The first one was a retrospective analysis of therapy algorithms used and excess weight loss. The second phase (included in this review data analysis) looked into prospective evaluation of selected therapy algorithms from phase 1. T2DM: Type 2 diabetes.

Table 6 Gastric Pacing studies summary

Ref.[1]	Sample size (enrolled/completed)	Mean age (yr)	Mean weight, (kg)/mean BMI (kg/m^2)	Follow-up (mo)	Lifestyle change (required/ advice given)
Cigaina *et al*[40], 2007	11/11	39.4 ± 3.4	121.7 ± 5.1/46.0 ± 2.5	8	N/Y
Liu *et al*[45], 2006	12/12	29.9 ± 12.3	58.6/21.4	3 d	NR/NR
Yao *et al*[42], 2005	12/12	29.4 ± 8.6	62.6 ± 8.3/23.18 ± 2.62	3 d	NR/NR
Cigaina *et al*[33], 2002	4/3 (1995/6 cohort)	31 ± 10	146 ± 25/55.9 ± 3	60	N/Y
Cigaina *et al*[33], 2002	10/10 (1998 cohort)	34.8 ± 8.6	142 ± 23.75/47.9 ± 5.8	30	N/Y
Cigaina *et al*[33], 2002	10/7 (2000 cohort)	41.8 ± 11.9	131.9 ± 33.1/51.41 ± 9.2	12	N/Y

[1]All trials were non-randomized.

the lesser or the greater curvature.

Regarding outcomes (Tables 8-10), almost all studies in each device group achieved statistically significant weight loss during the first 12 mo. However, only a very small proportion of studies had a follow-up longer than 1 year, and found significant weight loss maintenance.

Other outcomes included appetite or satiety changes and biochemical marker changes. Significant changes in reduction of Hb1Ac levels as well as blood pressure were evident in most TANTALUS® studies and in one IGS study.

Some outcomes were inconsistent. Two studies, one from TANTALUS®[39] and the other from gastric pacing[40], found lower ghrelin levels after device activation. However, three studies, two from IGS[41,42] and another TANTALUS®[43] study, found no statistically significant changes in ghrelin levels. Another interesting find was that 4 studies, including 2 RGES[41,44] studies and 2 gastric pacing[42,45] studies, demonstrated delayed gastric emptying whereas one TANTALUS® study demonstrated the opposite effect.

When the safety of the device implantation procedure was investigated, Transcend®-IGS studies reported the greatest number of device-related, non-medical complications. However, this may be due to the higher number of participants recruited in IGS studies. Gastric penetration was the most common complication during implantation. Even though it may seem to be a very serious complication, all studies reported that all gastric penetrations were corrected immediately and that no serious sequels were caused. Other important complications included lead dislodgement/lead failure and battery problems.

DISCUSSION

Gastrointestinal motility regulates the rates at which nutrients are processed and absorbed. It participates in controlling appetite and satiety *via* mechanical and neurohormone pathways. After bariatric surgery, morbidly obese patients experience reduced appetite and early satiety. These effects are probably related to endocrine effects of surgical procedures. Vertical banded gastroplasty increases post-meal cholecystokinin plasma levels, whereas Roux-en-Y gastric bypass inhibits basal and post-prandial ghrelin plasma levels and increases peptide YY (PYY) concentrations. Jejuno-ileal bypass increases cholecystokinin, motilin, glucagon-like peptide 1 and PYY, delays gastric emptying, and reduces hunger sensations.

As cholecystokinin, ghrelin and PYY also influence gastrointestinal motility, it can be hypothesized that the reduction of gastric emptying could well contribute to the satiety effect of the operations. All these data suggest that reducing gastric emptying could be beneficial for weight loss in patients who follow a strict hypocaloric diet. Modulation of gastric motility could well be a potential target to treat obesity and can be achieved through several means such as volume-occupying devices, intraparietal botox injection and induction of stomach "stiffness"[46-49].

Gastric electrical stimulation (GES) or gastric pacing data from animal models and preliminary data from human trials suggest that the gut-brain axis plays a role in the GES mechanism. This may involve the alteration of the secretion of hormones associated with hunger or satiety. Gastrointestinal tract hormones play a crucial role in regulating energy balance, and manipulation of gut endocrine activity through electrical signaling has been proposed as a potential therapy for obesity[50]. The effects of pacing may depend on stimulus parameters and stimulation sites[51]. Both the entrainment of intrinsic gastric electrical activity, eliciting propagating contractions and reducing symptomatology in patients with gastroparesis,

Table 7 Comparison of stimulation variables by different devices

Device (total number of studies)	Operation technique				Electrode implanted layer							Device active after n weeks				Type of pulse				Endoscopy			Postop image			
	L	O	E	NR	M	SM	Mus	SMus	SS	V	NR	0	⩽ 3 (1 ⩽)	4 ⩽	NR	Lo	T	NR	UC	Y	N	NR	XR	E-US	B	NR
TANTALUS® (8)	8	0	0	0	3	0	0	0	4		1	0	1	6	1	0	0	6	2	3	0	5	1	0	0	7
IGS-Transcend® (13)	12[1]	2[1]	0	1	0	0	2	4	1		5[2] (1[4])	0	4[3]	9[3]	0	0	9	3 (1[4])	0	7	5 (1[4])	0	5	1[5]	1[5]	7 (1[4])
RGES (3)	0	0	3	0	3[6]	3[6]	0	0	0		0	3	0	0	0	2[7]	2[7]	0	0	3	0	0	2	0	0	1
Vagal (3)	3	0	0	0						3	0	0	3	0	0	0	0	0	3	0	0	3	0	0	0	3
Pacing (4)	2[1]	2[1]	2	0	2[6]	1[6]	2	0	0		0	2	0	1	1	2[8]	1[8]	1	1	4	0	0	2	0	0	2
Total (33)	25	4	5	1	8	4	4	4	5	3	6 (1[4])	5	9	16	2	4	12	10 (1[4])	6	17	5 (1[4])	8	10	1	1	20 (1[4])

[1]Two studies implanted leads either by laparoscopic or open approach; [2]Two studies reported "gastric wall", but did not specify which particular layer; [3]One study activated its device after 3 or 4 wk, so each category was counted once; [4]No full text for LOSS trial, and this information was also not provided on another study, which reviewed this particular trial; [5]One study did both X-ray and endoscopic USS. Similarly another study did both X-ray and GI Barium test; [6]Implanted electrodes in mucosa and submucosa (3 studies in RGES; 1 study in Gastric Pacing); [7]One study carried out two different pulses; [8]One study carried out two different pulses. L: Laparoscopic; O: Open; E: Endoscopic; NR: Not reported; M: Mucosa; SM: Submucosa; Mus: Muscular; SMus: Seromuscular; SS: Subserosa; V: Vagal nerve; Lo: Long pulse; T: Train of short pulses; UC: Uncertain; Y: Yes; N: No; XR: X-ray; E-US: Endoscopic ultrasound scan; B: Gastrointestinal Barium test.

and reducing appetite and food intake in morbid obesity were suggested[52]. Additionally, gastric stimulations have extra gastrointestinal effects, including the alteration of systemic hormonal and autonomic neural activity and the modulation of afferent nerve pathways projecting to the central nervous system. These devices require a laparoscopic procedure to be implanted. Overall results suggest a short-term excess weight loss of approximately 40%[32].

The concept of electrical stimulation of electro-sensitive tissues is not new. It has been used for centuries in physiology studies and has a potential therapeutic strategy. Deep brain stimulation is used to treat Parkinson's disease. Neuromodulators can improve chronic non-malignant pain, and sacral nerve electrical stimulation can restore bladder function in refractory voiding dysfunction[53]. Colonic pacing has been used to induce rectal motility and evacuation in patients with colonic inertia, suffering from slow-transit constipation[54].

With much use of electrical stimulation in various medical fields in the past and recent promising results from many animal experiments, it appears that GES was the most effective and appropriate choice to reverse the increasing incidence of obesity and its related health co-morbidities.

Unlike cardiac pacemakers which can bring about a rapid response from cardiac muscles and nerves, the smooth muscles in the stomach slow down the response to electrical stimulation, forcing stimulations to have either longer or wider pulses[10].

In an experimental study, it was found that an intrinsic gastric pacemaker was present between the upper one third and lower two thirds of the stomach, on the upper part of the lesser curvature[55]. Gastric pacing at these locations has demonstrated the following effects: reduced appetite, increased satiety, inhibition of gastric motility. In addition, it directly affected central nervous system mechanisms and gastric hormones controlling satiety and appetite[55].

To date, several different types of GES have been developed. The most widely known commercial ones are the following[22]: (1) TANTALUS® system (MetaCure, Atir Yeda 17 Kfar Saba, Israël); (2) Enterra® Therapy (Medtronics, United States); (3) Transcend® Implantable Gastric Stimulator (Medtronic Transneuronix, United States); (4) Maestro® rechargeable system (EnteroMedics, United States)-electrical stimulation of the vagal nerve; and (5) Acupulser model A310, (World Precision Instrument, Sarasota, FL, United States)-Retrograde electrical stimulation.

The first human use of GES was for the treatment of gastroparesis in Tennessee in 1992, and its use for obesity soon followed in Italy in 1995[56]. While the GES device for the treatment of nausea and vomiting in patients with gastroparesis, called Enterra®, is FDA-approved, none of the GES devices have obtained FDA approval to treat obesity as of yet[57]. However, commercially available GES devices such as TANTALUS®, Transcend® and Maestro® are used clinically in Europe[56].

The exact mechanisms of action of GES are still unknown[24,26]. Some potential mechanisms of GES include a local enteric nervous system effect influenced by changes in gastric volume, an autonomic nervous system that can have different effects depending on frequency, a central nervous system and peptide hormonal changes in cholecystokinin (CCK), ghrelin, leptin, glucagon-like peptide-1 (GLP-1), and somatostatin[56,58].

Table 8 Comparison of outcomes of different devices (statistically significant outcomes only)

Device (total number of studies)	Significant weight loss achieved ≤ 12 mo (number of trials)	Follow-up beyond 12 mo and significant weight loss maintained from the first 12 mo (number of trials)[1]	Appetite reduction/satiety increase (number of trials)	Food and/or water intake reduction, comparing study group to control (number of trials)	Changes in gastric emptying (number of trials)	Biochemistry changes reported (number of trials)[4]
TANTALUS® (8)	6[2]	None (maximum of 12 mo follow-up)	2 (25%)		Increased (1)	4[5]
IGS-Transcend (13)	10[3]	5	3 (23%)			1
Vagal stimulation (3)	2	None (maximum of 12 mo follow-up)	3 (100%)			1
Gastric Pacing (6)	4	2		2	Delayed (2[6])	1
Total (30)	22	7	8 (26.6%)	3	5	7

[1]Maintained weight loss means that studies had shown significant weight loss during the first year of their follow-up; [2]One study showed a weight loss of 3.62% from baseline at 37 wk, but p value was not given, so this was not included in the count; [3]One study demonstrated significant weight loss at 12 mo only after procedural correction; [4]Significant biochemistry changes include any gastrointestinal hormones (such as ghrelin, peptide YY, leptin, somatostatin, cholecystokinin, Glucagon-like Peptide-1), HbA1c, fasting blood glucose, cholesterol; [5]One study showed a reduction of -12.2% in HbA1c levels at 37 wk but *P* value was not given so it was not included in the count; [6]In one study, gastric emptying was achieved only after 45 min, and there was no significant delaying afterwards.

In order to achieve weight loss, one or more of the following processes should be achieved by the neurohormones[50]: (1) GLP-1 (incretin hormone found in the lower gut) must be increased in response to food intake in order to delay gastric emptying; (2) Leptin (coded by the ob gene, found in adipose tissues) must be increased to induce food intake reduction, improve glucose homeostasis, and increase energy expenditure; and (3) Peptide YY (PYY, gut hormone found in L cell of lower intestine) changes its form to PYY 1-36 in fasting state and to PYY 3-36 in post-prandial state. Its increased level can inhibit gastric motility to reduce hunger and consequently reduce food intake. It also results in better glucose homeostasis, secondary to increased insulin sensitivity as well as reduction in triglyceride and fatty acid levels: (1) CCK (produced by endocrine cells in the small intestine) must be increased to reduce food intake *via* CCK-1 receptors in vagus nerves; and (2) Ghrelin (produced by cells in the oxyntic glands of the stomach and intestines) must be reduced to decrease food intake and lose body weight.

Ghrelin is the only known peripheral orexigenic peptide hormone[50,58]. If its level can be lowered, it can achieve appetite reduction, and therefore weight loss. A number of studies routinely measured ghrelin levels, but the results were inconsistent as some studies found significantly lowered ghrelin level after GES, while others failed to demonstrate any significant changes[36,43].

In the present review, we aimed to focus on GES devices and we tried to analyze available evidence on a larger group of GES devices to obtain a general overview. Globally, we found many variations and much heterogeneity in the reported studies concerning the type of device, stimulation parameters and outcomes. It was therefore difficult to report data in a standardized way, especially when trying to correlate stimulation parameters and outcomes.

Technical considerations

Implantation: The most common electrode implantation procedure was by laparoscopic surgery. Electrodes were most frequently implanted in the mucosa of the stomach wall. However, TANTALUS® and Transcend® were more frequently implanted in the submucosa and seromuscular layers. Generators were implanted in a subcutaneous pouch on the anterior abdominal wall. The mucosa has a higher impedance than the serosa, limiting the spread of electrical stimuli into muscular and neural networks in the stomach[22]. However, the correct placement through the different layers was checked by means of perioperative endoscopy, which can be less accurate than electrophysiology or image-guided testing (such as high frequency endoscopic ultrasound).

Stimulation parameters (Table 7): In general, participants were given 4 or more weeks of recovery time before starting the stimulation.

The "optimal stimulation pattern" has not yet been found. There are three stimulation methods-long pulse, short pulse, and trains of short pulses. The long pulse has the ability to "pace" or entrain a natural slow wave with a pulse width in the order of milliseconds and a frequency that is close to the physiological frequency of the gastric slow wave[10]. Gastric pacing uses long pulses but there are currently no implantable pulse generators that can produce pulses with a width longer than 2 milliseconds[10]. Long pulses generally improve symptoms of nausea and vomiting while having little effect on gastric motility. Conversely, long pulses improve gastric motility but are less effective when it comes to nausea and vomiting management[10].

Trains of short pulses consist in continuous short pulses with a high frequency (5-100 Hz) and a control signal to turn pulses on and off[10]. IGS-Transcend® by Medtronics uses this method to induce early satiety with subsequent reduction of food intake and weight loss, but it has failed to show consistent and positive weight loss in obese patients[57] and requires more powerful devices with a wider pulse width as suggested in one review[10,57]. Short

Table 9 TANTALUS® studies significant outcomes

	Weight, kg	Average Weight loss, kg (%)			HbA1c (%)	Average HbA1c reduction, % (% change)			Other statistically significant or important negative results[3]
	Baseline	At 3 mo ± 2 wk	At 6 mo ± 2 wk	At 12 mo ± 3 mo	Baseline	At 3 mo ± 2 wk	At 6 mo ± 2 wk	At 12 mo ± 3 mo	
T1[38]	110.5 ± 3.5		-5.38 (-4.87%), P < 0.01		8.3% ± 0.12%		-1.0 (-12.0%), P < 0.001		Lower BP (S/D)
T2[70]	107.7 ± 21.1 (n = 11)	-3.00 (-2.79%), P < 0.05	-5.30 (-4.92%), P < 0.05		8.5% ± 0.7%	-1.0 (-11.8%), P < 0.05	-0.9 (-10.6%), P < 0.05		Lower BP (S) Lower total cholesterol Lower LDL
T3[39]	123.7 ± 4.5		-5.80 (-4.70%), P < 0.05 at 5 mo	-4.50 (-3.70%) [P < 0.05]	8.0% ± 0.2%		-0.6 (-7.5%), P < 0.05 at 5 mo	-0.5 (-6.3%), P < 0.05	Lower FBG Lower ghrelin[4] Higher adiponectin[4] Reduced appetite[2] (P < 0.05)
T4[37]	NR		-5.50 (P < 0.01)		8.4% ± 0.1%		-1.1 (-12.1%), P < 0.01		Lower BP if hypertensive at baseline
T5[71]	104.4 ± 4.4	-4.70 (-4.52%), P < 0.001			8.0% ± 0.2%	-1.1 (-12.8%), P < 0.001			Lower BP (S/D) Lower FBG
T6[69]	130 ± 6.5			-4.70 (-3.62%) (P value NR) at 37 wk	8.2% ± 0.2%			-1.0 (-12.2%) (P value NR) at 37 wk	
T7[43]	NR								Increased GE Reduced gastric retention (No significant changes in Ghrelin)
T8[72]	128.8 ± 5.2		-8.90 (-6.91%), P < 0.05 at 5 mo	-16.4 (-12.7%) (P value NR)[1]					Lower BP if hypertensive at baseline Reduced appetite (P < 0.05)

[1]Only 9 out of 12 subjects remained by the 12th month; [2]Except from week 20 to week 52, there was a slight increase (P = NS) in hunger score, but otherwise, all scores were significant (P < 0.05); [3]Significant results in reference to baseline values; [4]Results based on a smaller subset of participants. BP: Blood pressure; LDL: Low-density lipoproteins; FBG: Fasting blood glucose.

pulses or trains of short pulses fall into the category of low energy/high frequency stimulation which does not entrain slow wave or improve gastric emptying. High energy/low frequency stimulation does entrain slow wave or correct gastric dysrhythmia, but it does not allow for the potential improvement of gastric emptying. However, as abovementioned, there is no commercially available implantable long pulse device as of yet[59]. Enterra® uses short pulses, namely a pulse width of a few hundred microseconds, and a frequency higher than the physiological frequency of the gastric slow wave[60]. Commercially available cardiac pacemakers or nerve stimulators also use short pulses.

Different types of stimulation also have varying effect on weight loss. Antegrade stimulation propagates its impulses in a forward direction, and works more effectively on the gastroparetic stomach. On the other hand, retrograde stimulation affects conduction of slow wave activity of the gastric smooth muscle in the opposite direction to antegrade, thereby slowing gastric emptying and inducing more active weight loss. However, it all depends on the setting. The technical aspects of devices are not discussed in this review as they have been extensively tackled previously in other recent reviews on GES.

General considerations on studies and outcomes of the most relevant studies

The level of evidence is generally quite low. Most studies were non-randomized trials and only a few studies had a large population size with low drop-out rates. Many studies included either healthy volunteers or subjects who only had obesity. In contrast, TANTALUS® studies included obese patients with co-morbidities such as type 2 diabetes and hypertension. As a consequence, the majority of TANTALUS® studies reported on HbA1c levels in addition to weight loss (Table 9).

Weight loss was the primary outcome, but follow-up generally lasted less than 12 mo and maintenance of significant weight loss was rarely observed. Only one study[28,39] reported significant weight loss at both 6 and 12 mo. However, 6-mo weight loss was greater than that achieved at a later time period. This might mean that GES may not induce long-term weight loss and that some patients may lose weight due to other variables such as postoperative effects.

One valuable screening tool is the Baroscreen™, trademarked by Medtronic Transneuronix, Inc. The Baroscreen™ is a computer software which measures the suitability of obesity therapy through a mathematical algorithm and allows to select patients who are most likely to lose ⩾ 15% excess bodyweight within 12 mo. The Baroscreen™ was applied to some Transcend®-IGS studies (n = 4). In two studies[15,28], significant weight loss was observed while in other studies[21,29] no significant weight loss was reported. Some of the IGS studies also required their subjects to have a specific diet and exercise regimen,

Table 10 Implantable Gastric Stimulator Transcend® outcomes

	Weight, kg	Average Weight loss, kg (%)-In the treatment group compared to baseline weight				Hunger reduction/ Reduced appetite	Other statistically significant or important negative results[3]
	Baseline	At 3 mo ± 2 wk	At 6 mo ± 2 wk	At 12 mo ± 3 mo	Beyond 12 mo		
I1[28]	113.1		-7.0 (-6.2%), $P < 0.05$	-5.5 (-4.9%), $P < 0.05$	-2.1 (-1.9%), $P < 0.05$ at 24 mo		In control group, weight gain despite IGS activation from 12 to 24 mo No significant change in fasting ghrelin or Peptide YY levels
I2[21]	NR						No significant weight loss observed
I3[73]	112.5		-2 (-1.8%) NS	+3.5 (+3.1%) NS			No significant weight loss observed
I4[29]	92		%EWL = 5.9%				
I5[30]	116	%EWL = 14%	%EWL = 19%	%EWL = 20%	%EWL = 25%		
I6[20]	129		%EWL = 1.3% (study group); 2.4% (control) NS	Mean %EWL = 2.5% (P value NR)	%EWL = 20% at 29 mo[1]		Only a subset (23%) of patients lost significant amount of weight (> 5% EWL)
I7[20]	NR			%EWL > 10% in 54% of subjects; > 20% in 23%	%EWL = 23% at 16 mo	Yes[2], $P = 0.0433$	Satiety increased between and at the end of meals
I8[32]	132.7± 27.3	%EWL for 2 yr period for each cohort = 20%-40%					Lower blood pressure
I9[74]	115	%EWL = 16.3% -8.2 (-7.11%), $P = 0.0011$	%EWL = 16.9% -8.4 (-7.29%), $P = 0.0310$	%EWL = 23.8% at 10 mo -11.7 (-10.1%), $P = 0.0112$		Yes	Satiety increased between and at the end of meals
I10[36]	115	%EWL = 15.8%	%EWL = 17.8%	%EWL = 21.0% at 10 mo	%EWL = 21.0% at 15 mo	Yes	Satiety increased between and at the end of meals No significant change in ghrelin level
I11[75]	121.7± 5.1		-10.4 (-8.5%), $P < 0.01$				Reduced meal-related CCK response Lower basal and meal-related somatostatin level Lower basal GLP-1 level (Not meal-related) Lower basal leptin level (Not meal-related)
I12[35]	NR			-2.7%, $P = 0.03$			Significant weight loss at 12 mo was observed after procedural corrections
I13[76]	122.2	%EWL = 17.8% -9.4 (-7.7%) (P value NR)	%EWL = 18.6 -10.0 (-8.2%) (P value NR)	%EWL 30.2 at 9 mo -16.0 (-13.1%) (P value NR)			

[1]Very small number of remaining subjects ($n = 34$); [2]Responses to the Satiety and Dietary Analysis Questionnaire; [3]Significant results in reference to baseline values. NR: Not reported; EWL: Excess weight loss; CCK: Cholecystokinin; GLP-1: Glucagon like peptide-1.

but this did not mean that the outcome was necessarily better. Two studies[21,28] required patients to have a 500 kcal/d deficit diet, and participate in monthly support group meetings. One study[29] required a 500 kcal/d deficit diet with an exercise program. Another[20,31] required patients to complete the LEARN Behavior Modification Program and to attend monthly support group meetings. Diet and behavior modification had only a very mild short-term impact. Considering that diet and exercise only have a short-term effect, it is logical to assume that its effect on weight loss may be negligible in the long term.

Generally speaking, the majority of bariatric interventions, whether surgical or not, including procedures for GES device implantation, induce effective short-term weight loss. Therefore, follow-up periods to assess weight loss modalities should be relatively long to eliminate confounding effects from any dietary or behavioral change that some patients may undergo at the beginning of their treatment.

An additional problem with long-term follow-up is that in battery-operated devices, the battery may run out and lead to weight regain[24]. In a case series, patients followed up for approximately 10 years underwent repeated surgery for battery replacement[61]. Battery lifetime is approximately 2 to 5 years, which implies inevitable repeated procedures in relatively short intervals[11]. An improvement of battery technology for longer-lasting batteries and in the battery life monitoring method, are clearly required in order to sustain long-term weight loss,

and enhance the role of GES in obesity.

Other commonly reported outcomes included appetite reduction/satiety increase, gastric emptying rate change and gastric hormonal or other biochemical markers such as ghrelin and HbA1. Blood pressure was also monitored in the majority of TANTALUS® and in some Transcend® studies. In almost all cases, the decrease in blood pressure was more pronounced if patients were hypertensive at the start of the trial. This led to a theory that GES influences the autonomic nervous system[32] but the exact physiology has not been studied.

Safety and adverse events

Despite the fact that GES implantation is less invasive than bariatric surgery, it still requires an operation with general anesthesia. Although all devices were deemed to be safe as there were no serious complications or deaths from procedures, the absolute numbers for device-related complications such as gastric penetration and lead dislodgement were relatively high. Out of the two complications, gastric penetration was the most frequent one. It appeared to happen more often when the implantation involved either the subserosa or seromuscular layers. Gastric penetrations were corrected surgically in all cases, and no further serious complications occurred postoperatively. This potential complication stresses the need for intraoperative endoscopy during or after lead implantation as a crucial part of the procedure[62]. Postoperative complications such as nausea, constipation, and hypoglycemia were rare and could be minimized by careful monitoring, and by optimizing medical treatments, controlling pain with analgesics and assessing the functional status of each patient properly prior to discharge[62].

Other forms of electrical stimulations have also been reported in the literature. Intestinal electrical stimulation (IES) is used in the duodenum or the colon. It affects intestinal slow waves, contractions and transit through vagal and cholinergic and adrenergic pathways[22]. Just like GES, there are various types of pulses for IES such as long pulse, short pulse, train of short pulses, dual pulses and synchronized pulse stimulation. Numerous studies have been carried out mainly in canine subjects while only two studies[63,64] were performed in humans. One study demonstrated accelerated intestinal transit and reduced absorption in patients with lipid infusion[63], and another demonstrated delayed gastric emptying and reduced gastric accommodation[64]. In animal experiments, more comprehensive effects were observed. In rats, IES reduced food intake and bodyweight in both lean and obese rats, decreased ghrelin levels and increased CCK in duodenal tissues[65]. In dogs, IES induced gastric distension, which then reduced food intake[65].

In contrast to GES, IES uses repetitive long pulses with a frequency lower than 1 Hz in order to accommodate slow response time of intestinal smooth muscle to electrical stimulation[66]. It has been shown to entrain intrinsic intestinal slow waves and improve intestinal slow wave dysrhythmia in animals, but due to the lack of data from patients, more clinical trials must be performed before determining its effectiveness as a therapy for obesity[66].

Recommendations and future perspectives

The concept of gastric electrical stimulation itself seems to hold some promises. However, it has so far been shown that weight loss with GES is lower than that observed with current bariatric surgeries, but greater than that achieved with non-medical and behavioral modifications[67]. There are too many differences in the studies performed to date: different device parameters, different implantation sites and outcomes measured. This can only lead to a situation where studies are not comparable and high quality studies on GES and obesity do not exist to this date. The main reason to perform clinical trials on GES is to prove that GES is not inferior to bariatric surgery, which is the only effective treatment, but carries more risks due to the invasive nature of surgical procedures[68].

However, in order to be effective, GES should be tailored to each patient. The main drawback in the performed studies, from a purely physiological standpoint, is that electrodes are placed "somewhere" in the stomach where the pacemaker is supposed to generate contraction waves. It would be correct to generate the hypothesis that gastric pacemaker location varies from one patient to another, as well as sensitivity of the pacemaker to electric stimuli. The introduction of functional imaging modalities are generated, such as real-time Magnetic Resonance Imaging or intragastric electrode which allow to exactly locate the waves could well optimize the placement of electrodes or other different stimulation/blocking modalities.

Larger populations should be included in prospective trials in which electrical pulse properties and anatomical stimulation sites have been pre-determined in each patient prior to the procedure. Inclusion criteria should also be standardized, for example using tools such as the Baroscreen™, in order to stratify patients and obtain results which could be compared with other studies[52]. The follow-up period must be longer to minimize any placebo effect[69] and to prove that weight loss can be maintained for a longer period of time than weight loss induced by non-medical and medical interventions.

In addition, a GES device monitoring tool should be considered to improve the ease of use and the interaction between the device and patients, similarly to a cardiac pacemaker that patients can monitor using a telephone[54]. In terms of GES device, the ideal device should ultimately be implantable endoscopically (without having to undergo general anesthesia or any form of surgery), it should control the electrode and stimulation generator wirelessly in order to be connected without having to externalize the wire, and as mentioned above, stimulation parameters should be controlled and be recorded by a portable device that people could carry around with them, such as a mobile phone.

This systematic review presents the most up-to-date review of the literature on the effects that different GES devices have on obesity. Although not all the studies have shown consistent results, many studies have demonstrated that GES is effective for short-term weight control as well as for the change of other variables associated with obesity. However, well-designed, standardized clinical trials with a larger sample size and a longer follow-up period should be considered to prove its true benefit for the treatment of obesity and further advancement in GES device technology should continue to take place.

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COMMENTS

Background

Overweight and obesity, as a major health concern, have become a global issue. Lifestyle and medical measures are effective in the short term but maintenance of weight loss in the long term has proven to be difficult. On the other hand, surgical interventions are more effective in the long run but they have a higher risk of complication rates.

Research frontiers

Gastric Electrical Stimulation (GES) has shown to be more effective than lifestyle and medical options to treat obesity while having a lower risk of complications than bariatric surgery. The first use of GES was to treat gastroparesis in 1992, and its use for obesity soon followed in Italy in 1995.

Innovations and breakthroughs

GES for obesity is a method of provoking gastric contractions and inducing longer retention of food in the stomach to cause early satiety and therefore reduce food intake. Currently, there are many commercially available GES devices used clinically mostly in Europe. However, they do not benefit from FDA approval. Due to a wide range of existing devices with much variation in their type, stimulation parameters and study outcomes, it is difficult to report the combined data in a standardized way. Clinically, weight loss was achieved in most studies especially during the first 12 mo and studies with a longer follow-up period showed promising results in maintaining weight loss. Other positive outcomes reported were increase in satiety, decreased gastric emptying rate, reduced blood pressure, and changes in neurohormone or biochemical marker levels such as ghrelin or HbA1c.

Applications

This systematic review is the most up-to-date summary of the literature on the effects that different GES devices have on obesity by comparing their study designs, stimulation parameters, and reported outcomes. It also suggested that future studies should consider putting forward stronger evidence concerning GES benefit on obesity and making further advancements in GES technology.

Peer review

In this study, the authors made a systemic review on the GES to treat obesity, which evaluated the current state of GES application in clinic for treating obesity. It provided benefited reference for the clinical physicians and scientists.

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CLINICAL TRIALS STUDY

Analysis of YouTube™ videos related to bowel preparation for colonoscopy

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Abstract

AIM: To examine YouTube™ videos about bowel preparation procedure to better understand the quality of this information on the Internet.

METHODS: YouTube™ videos related to colonoscopy preparation were identified during the winter of 2014; only those with ≥ 5000 views were selected for analysis (n = 280). Creator of the video, length, date posted, whether the video was based upon personal experience, and theme was recorded. Bivariate analysis was conducted to examine differences between consumers *vs* healthcare professionals-created videos.

RESULTS: Most videos were based on personal experience. Half were created by consumers and 34% were ≥ 4.5 min long. Healthcare professional videos were viewed more often (> 19400, 59.4% *vs* 40.8%, P = 0.037, for healthcare professional and consumer, respectively) and more often focused on the purgative type and completing the preparation. Consumer videos received more comments (> 10 comments, 62.2% *vs* 42.7%, P = 0.001) and more often emphasized the palatability of the purgative, disgust, and hunger during the procedure. Content of colonoscopy bowel preparation YouTube™ videos is influenced by who creates the video and may affect views on colon cancer screening.

CONCLUSION: The impact of perspectives on the quality of health-related information found on the Internet requires further examination.

Key words: Colon cancer prevention; Bowel preparation; Colonoscopy; Screening; YouTube™; Social media

Core tip: YouTube™ is a major media channel viewed by millions each day. Despite this reach, there is a paucity of research on the nature and scope of communications related to cancer prevention and control. To our knowledge, this is the first published study analyzing communications through YouTube™ concerning bowel preparation. The content of the YouTube™ videos regarding colonoscopy bowel preparation is influenced by who creates the video. Consumer posted videos generated the majority of comments on this topic.

Basch CH, Hillyer GC, Reeves R, Basch CE. Analysis of YouTube™ videos related to bowel preparation for colonoscopy. *World J Gastrointest Endosc* 2014; 6(9): 432-435 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i9/432.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i9.432

INTRODUCTION

The Internet has become an increasingly popular source

of health information for consumers. With over half of United States Internet users searching for information on a specific medical procedure, the quality of information available and its impact on the public's thoughts are significant[1]. YouTube™ has monthly traffic volume of about 1 billion users and provides a unique platform for conveying health information where both consumer and professional videos can be accessed[2]. Despite widespread reach, limited research on this communication channel has been conducted to characterize the source and content of information conveyed.

The purpose of this study was to analyze source and content of information conveyed in frequently viewed YouTube™ videos about preparing for a colonoscopy. Colon cancer screening is an important preventive measure, which is recommended by the United States Preventive Services Task Force[3]. The American College of Gastroenterology has recommended CRC screening by colonoscopy as the preferred screening modality[4]. Despite the existence of these recommendations, rates of CRC screening in general and colonoscopy screening in particular are less than optimal[5]. One reason for this may be that preparing for a colonoscopy is typically considered the "worst part" of the colonoscopy procedure[6]. Inadequate bowel preparation, which has been shown to occur in as many as 20% of colonoscopies[7], can obscure vision, and pre-cancerous or cancerous polyps can be missed[7,8].

MATERIALS AND METHODS

Between January and February 2014, the YouTube™ website was searched using the following keywords: colonoscopy preparation (19000 videos), colonoscopy prep (5140 videos), colon prep (7570 videos), colon preparation (7950 videos), bowel preparation (1770 videos) and bowel prep (7770 videos). All videos were sorted to determine how many had over 5000 views and duplicate videos were removed (n = 280). Videos with the highest number of views were screened to verify that the focus was on preparation for colonoscopy. The source of each video was coded as being created by a consumer or a professional. We identified 98 videos created by consumers and 96 videos created by professionals that had ⩾ 5000 views, which were selected for analysis. These videos were coded based on total number of views received and subject matter. Subject matter coding included whether the topic was addressed by relating a personal experience, general information, completing the preparation, types of preparation, palatability, pain, time required, disgust, embarrassment, sleep deprivation, hunger, difficulty and fear. The length of each video was documented along with the time elapsed since it was uploaded and the number of comments recorded. These methods were piloted on 10 videos with fewer than 5000 views, which were not included in our sample. Coding of the videos was conducted by one of the authors (RFR) and by another author (CHB) for the 50 videos that received the most views. High inter-rater reliability was demonstrated using Cohen's Kappa (k = 0.89).

Table 1 Characteristics of YouTube™ videos (n = 194) of colonoscopy bowel preparation n (%)

	Total (n = 194)	Consumer (n = 98)	Healthcare professional (n = 96)	P value
Year video uploaded				0.14
2006	5 (2.6)	4 (4.1)	1 (1.0)	
2007	14 (7.2)	7 (7.1)	7 (7.3)	
2008	25 (12.9)	12 (12.2)	13 (13.5)	
2009	48 (24.7)	25 (25.5)	23 (24.0)	
2010	29 (14.9)	10 (10.2)	19 (19.8)	
2011	39 (20.1)	16 (16.3)	23 (24.0)	
2012	25 (12.9)	18 (18.4)	7 (7.3)	
2013, 2014	9 (4.6)	6 (6.1)	3 (3.1)	
Time since posting (mo)				0.31
0-36 (2011-2014)	73 (37.6)	40 (40.8)	33 (34.4)	
37-48 (2010)	29 (14.9)	10 (10.2)	19 (19.8)	
49-60 (2009)	48 (24.7)	25 (25.5)	23 (24.0)	
> 60 (2006-2008)	44 (22.7)	23 (23.5)	21 (21.9)	
Length of video (min)				0.45
0.0-1.5	46 (23.7)	21 (21.4)	25 (26.0)	
1.6-3.0	42 (21.6)	18 (18.4)	24 (25.0)	
3.1-4.5	40 (20.6)	23 (23.5)	17 (17.7)	
> 4.5	66 (34.0)	36 (36.7)	30 (31.3)	
Number of video views				0.037
5028-13300	48 (24.7)	32 (32.7)	16 (16.7)	
13301-18400	49 (25.3)	26 (26.5)	23 (24.0)	
18401-66500	49 (25.3)	20 (20.4)	29 (30.2)	
66501-3933235	48 (24.7)	20 (20.4)	28 (29.2)	
Views per month				0.18
0-250	52 (26.8)	32 (32.7)	20 (20.8)	
251-500	40 (20.6)	21 (21.4)	19 (19.8)	
501-2000	59 (30.4)	28 (28.6)	31 (32.3)	
> 2000	43 (22.2)	17 (17.3)	26 (27.1)	
Number of comments				0.001
0-3	53 (27.3)	16 (16.3)	37 (38.5)	
4-9	39 (20.1)	21 (21.4)	18 (18.8)	
10-40	44 (22.7)	31 (31.6)	13 (13.5)	
> 40	58 (29.9)	30 (30.6)	28 (29.2)	
Comments per month				0.09
< 1	130 (67.0)	60 (61.2)	70 (72.9)	
1-2	26 (13.4)	18 (18.4)	8 (8.3)	
> 2	38 (19.6)	20 (20.4)	18 (18.8	

Descriptive analyses included frequencies, percentages, means, standard deviations, and ranges. Length of time since posting in months, length of the video in minutes, number of views, overall and per month, and total number comments were grouped by quartile. Analysis was performed using Chi-square for categorical variables and ANOVA for continuous variables. One-sided p values < 0.05 were considered statistically significant. All analyses were performed using IBM SPSS (version 21). All study procedures were reviewed by the institutional review boards of the authors' respective institutions and were deemed not related to human subjects.

RESULTS

Consumers and healthcare professionals each created approximately one-half of the videos (Table 1). Videos

Table 2 Themes of YouTube™ videos *n* (%)

	Total (*n* = 194)	Consumer (*n* = 98)	Healthcare professional (*n* = 96)	*P* value
Based on personal experience				0.18
Yes	114 (58.8)	53 (54.1)	61 (63.5)	
No	80 (41.2)	45 (45.9)	35 (36.5)	
Themes				
General information				< 0.001
Yes	79 (40.9)	12 (12.4)	67 (69.8)	
No	114 (59.1)	85 (87.6)	29 (30.2)	
Completing the preparation				< 0.001
Yes	43 (22.2)	11 (11.2)	32 (33.3)	
No	151 (77.8)	87 (88.8)	64 (66.7)	
Types of preparation				< 0.001
Yes	20 (10.3)	3 (3.1)	17 (17.7)	
No	174 (89.7)	95 (96.9)	79 (82.3)	
Palatability				0.048
Yes	55 (28.4)	34 (34.7)	21 (21.9)	
No	139 (71.6)	64 (65.3)	75 (78.1)	
Pain				0.78
Yes	23 (11.9)	11 (11.2)	12 (12.5)	
No	171 (88.1)	87 (88.8)	84 (87.5)	
Time involved				0.68
Yes	49 (25.3)	26 (26.5)	23 (24.0)	
No	145 (74.7)	72 (73.5)	73 (76.0)	
Disgust				0.009
Yes	19 (9.8)	15 (15.3)	4 (4.2)	
No	175 (90.2)	83 (84.7)	92 (95.8)	
Embarrassment				0.08
Yes	17 (8.8)	12 (12.2)	5 (5.2)	
No	177 (91.2)	86 (87.8)	91 (94.8)	
Sleep deprivation				0.06
Yes	10 (5.2)	8 (8.2)	2 (2.1)	
No	184 (94.8)	90 (91.8)	94 (97.9)	
Hunger				0.009
Yes	19 (9.8)	15 (15.3)	4 (4.2)	
No	175 (90.2)	83 (84.7)	92 (95.8)	
Difficulty to perform				0.65
Yes	18 (9.3)	10 (10.2)	8 (8.3)	
No	176 (90.7)	88 (89.8)	88 (91.7)	
Fear				0.71
Yes	26 (13.4)	14 (14.3)	12 (12.5)	
No	168 (86.6)	84 (85.7)	84 (87.5)	

were uploaded between 2006 and 2014, with the majority (79.3%) posted after 2008. Just over one-third of the videos were > 4.5 min (SD 5.3) in length (range 0.4 to 53.3 min), with the remaining videos distributed fairly evenly across the three other categories. Combined, there were more than 12.7 million views of the sampled videos. The number of views per video varied greatly and was dependent upon the length of time the video was available for viewing (overall range 5028 to 3.9 million views, range per month 91 to 57003). The number of comments also differed widely overall, ranging from no comments posted to nearly 3000. The mean number of comments per month was 1.3 (SD 4.1).

Overall, healthcare professional-generated videos had greater numbers of views than did those created by consumers (> 19400, 59.4% *vs* 40.8%, $P = 0.037$, for healthcare professional and consumer, respectively). In contrast, videos created by consumers received more comments (> 10 comments, 62.2% *vs* 42.7%, $P = 0.001$). When examining the number of views and comments per month, this difference was no longer observed. Additionally, no differences between videos created by consumers *vs* healthcare professionals were observed for the year of posting or length in minutes.

Almost 60% ($n = 114$) of all of the videos sampled were based on personal experience, and there was no significant difference regarding this appeal based on the source of the communication (Table 2). Compared with consumer created videos, those created by healthcare professionals were much more likely to provide general information about the preparation process, (12.4% *vs* 69.8%, $P < 0.001$), include information about completing the preparation process (11.2% *vs* 33.3% $P < 0.001$), and the types of preparation options that are available (3.1% *vs* 17.7% $P < 0.001$). Overall, only approximately 10% of the videos addressed the different types of preparation purgatives, disgust, embarrassment, hunger, difficulty, and fear and only approximately 5% dealt with the topic of sleep deprivation. There were no significant differences between the videos created by consumers *vs* healthcare professionals with respect to palatability of the purgative, pain, time involved, embarrassment, sleep deprivation, difficulty, and fear. In contrast, compared with videos created by healthcare professionals, those created by consumers were more likely to address topics related to palatability of the purgative (21.9% *vs* 34.7%, $P < 0.05$), disgust (4.2% *vs* 15.3%, $P < 0.01$), and hunger (4.2% *vs* 15.3%, $P < 0.01$).

DISCUSSION

The clinical and public health benefits of colonoscopy screening can be compromised by poor quality preparation[7,9-11] as well as adding cost, risk and inconvenience due to repeated procedures[12]. Suboptimal preparation is not a rare occurrence[13,14] and appears to be more likely among those at greater risk for late stage of diagnosis and consequently worse prognosis[13]. Efforts to promote adequate (or ideally optimal) preparation are, therefore, warranted. Social media such as YouTube™ is a communication channel that is increasingly used by the public to acquire health information in general and colonoscopy preparation specifically.

This was the first study to assess colonoscopy preparation information on YouTube™. This sample of videos collectively had nearly 13 million views. Many of the videos were related to personal experience. Some important topics (*e.g.,* types of preparation purgatives, disgust, embarrassment, hunger, difficulty, fear and sleep deprivation) were not addressed by majority of the videos reviewed. Social media has both the promise of reaching a very large audience with important information, but may also provide misinformation. Even if the information conveyed is accurate, it may negatively influence views on colon cancer screening. Future studies are needed to verify the accuracy of information about colonoscopy

preparation and to assess the perspectives conveyed. Social media is currently underutilized by governmental agencies to convey important health information about colonoscopy preparation and this is a missed opportunity to provide accurate and accessible information to the public about this important public health topic.

COMMENTS

Background

Colonoscopy has emerged as the preferred colon cancer screening method. Bowel preparation for colonoscopy has been described as the worst part of the procedure. Many people seek health information from media outlets like YouTube™.

Research frontiers

To date, there are no published papers examining the content of these videos related to bowel preparation for the colonoscopy procedure.

Innovations and breakthroughs

There were no other studies on this topic identified in the published literature. This is an innovative study in that it is the first in the published literature to analyze source and content of information conveyed in frequently viewed YouTube ™ videos about preparing for a colonoscopy.

Applications

The practical applications of these findings are that endoscopists should be aware of misinformation that may impact beliefs and practices of a patient regarding colonoscopy preparation.

Terminology

YouTube™ is a popular video-sharing web site based in the United States.

Peer review

The results of present study have new and original finding. The study has been thought very well and its design is good.

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SYSTEMATIC REVIEWS

Evaluation of surgical training in the era of simulation

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Abstract

AIM: To assess where we currently stand in relation to simulator-based training within modern surgical training curricula.

METHODS: A systematic literature search was performed in PubMed database using keywords "simulation", "skills assessment" and "surgery". The studies retrieved were examined according to the inclusion and exclusion criteria. Time period reviewed was 2000 to 2013. The methodology of skills assessment was examined.

RESULTS: Five hundred and fifteen articles focussed upon simulator based skills assessment. Fifty-two articles were identified that dealt with technical skills assessment in general surgery. Five articles assessed open skills, 37 assessed laparoscopic skills, 4 articles assessed both open and laparoscopic skills and 6 assessed endoscopic skills. Only 12 articles were found to be integrating simulators in the surgical training curricula. Observational assessment tools, in the form of Objective Structured Assessment of Technical Skills (OSATS) dominated the literature.

CONCLUSION: Observational tools such as OSATS remain the top assessment instrument in surgical training especially in open technical skills. Unlike the aviation industry, simulation based assessment has only now begun to cross the threshold of incorporation into mainstream skills training. Over the next decade we expect the promise of simulator-based training to finally take flight and begin an exciting voyage of discovery for surgical trainees.

Key words: Simulation; Surgical training; Surgery; Training; Objective Structured Assessment of Technical Skills; Observational tool; Surgical skills; Assessment; Skill assessment

Core tip: The nature of surgical training has teetered on the brink of a seismic change in how we can deliver the level of expertise required of a modern surgeon for over a decade. It is evolving from Halstedian's apprenticeship model towards simulation-based training similar to the aviation industry. Since 2000 there have been approximately 173 studies about validation of simulators as assessment tools. As the technology grows, its translation into real changes in curriculum is still unclear. This review is focused upon where we currently stand in relation to the effective integration of simulation-based skills assessment into modern surgical training curricula.

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INTRODUCTION

The nature of surgical training has teetered on the brink

of a seismic change in how we can deliver the level of surgical training required of a modern surgeon for over a decade. The demands imposed by a zero complication ethos expected by patients and emphasised by the media has challenged us as surgical educators to continually assess our training paradigms. Traditionally, surgical training has been largely an opportunity-based learning approach based upon an apprenticeship in the operating room (OR). This Halstedian method[1] of surgical training is often exemplified as the "see one, do one, teach one" approach to training. This system which was reliant upon opportunistic encounters particularly of the complex case mix variety remains extremely time dependant. This apprenticeship model resulted in surgical training often being prolonged in order to gain sufficient surgical experience to reach a subjective level of operative experience. In the modern era of surgical training, trainees are continually restricted on the number of hours they can legally work. This may be as low as 48 h per week in Europe[2] or 80 h in North America[3]. These mandated reductions in working hours have been based upon safe guarding both patients and doctors alike in order to decrease potential errors in the health care system. This decrease in hours however will result in a fundamental reduction in the trainees' opportunity for surgical operating time exposure with "real" patients. As a direct consequence of these challenges, interest in laboratories with formal curricula, specifically designed to teach surgical skills, has increased dramatically[4].

The use of surgical simulators and inanimate bench models for training and assessment has been the centre of attraction among the training bodies around the world for well over a decade. The use of simulation for clinical skills training, assessment and clinical scenario management provides educators the freedom of focused training in more controlled environment without risking the life of any patients. Trainees may also have the chance to practice the skills required of a modern surgeon to proficiency at their own pace. The greatest advantage of virtual reality medical simulation is the opportunity to try and fail without consequence for the patient[5]. The integration of simulation into training programmes would therefore seem the next most intuitive step for the design and implementation of any modern surgical training curriculum.

In tandem with the continued development of surgical skills in training surgeons of equal importance is our ability to assess the candidates' proficiency in the performance of these very surgical skills that we have taught. Once again the assessment of surgical skills has been largely subjective and onto this horizon surgical simulation may also provide a solution. The objective characterisation of technical skills can be difficult. Technical performance assessment ranges from basic surgical skills such as knot tying and suturing, basic laparoscopic skills and endoscopy to a wide spectrum of evaluations that include performing complex procedures such as laparoscopic cholecystectomy, vessel anastomosis and tendon repair. Assessment can be defined as making a judgement against a predefined reference[6]. As surgical educators, it is important to assess trainees on their progress in surgical skills in order to ensure that they remain safe in the stressful environment of a real operating theatre. It allows the trainers to give a constructive feedback based on their performances and can be used for the award of certification or even credentialing. Despite its importance to surgeons, technical proficiency historically has been poorly evaluated[7]. A good assessment tool must possess reliability, validity, educational impact, acceptability and feasibility[8].

The aim of this review is to determine where we currently stand in relation to the use of simulation in surgical skills assessment within current training curricula. We focused upon the use of simulators in surgical curricula that embraced the concept of creating proficiency profiles using simulators. Technical performance assessment in laparoscopy, endoscopy and open surgical skills were included.

MATERIALS AND METHODS

This review encompassed a literature search in PubMed from January 2000 to November 2013. The keywords used to search the database were "simulation", "skills assessment" and "surgery". All search result titles and abstracts were reviewed by the authors, SS and PN. Full texts of compatible articles were examined for eligibility of inclusion as agreed by the two authors.

Inclusion criteria

Studies were included if simulators were used in laparoscopic and endoscopic skills assessment following an intervention such as skills training, courses, surgical curriculum and selection process. Also, studies using simulators to assess open technical skills such as knot tying, suturing or a basic open procedure, for example excisions of sebaceous cyst were included.

Exclusion criteria

The review was focused upon the use of simulators in assessment of surgical skills. Studies that aimed at validating their latest simulator alone were excluded. Studies were excluded if the surgical skills are of specific subspecialties such as ophthalmology, urology, gynaecology, cardiothoracic, ear, nose and throat (ENT), neurosurgery, trauma and orthopaedics, as well as non-validated methods, non-technical skills for example cognitive analysis and patient care simulation. Any non-English articles, reviews, conference abstracts, editorial, comments, supplements and case reports were excluded.

RESULTS

The keyword search yielded 515 articles, of which 201 articles were eligible. Following the application of our inclusion and exclusion criteria, there were 52 articles

Table 1 Study characteristics assessing open surgical skills (n = 5)

Ref.	Year	No. of trainees	Tasks	Assessment tool
Acton *et al*[9]	2010	157 clerkship	Suturing	OSATS
Brydges *et al*[10]	2008	38 trainees	One-handed knot tying	Motion analysis (ROVIMAS) and GRS
Chipman *et al*[11]	2009	24 trainees PGY 1	Excision of skin lesion and wound closure	OSATS
Jensen *et al*[12]	2008	45 PGY 1-2	Excision of skin lesion and bowel anastomosis	Video-based OSATS and FPA (wound closure aesthetic quality and anastomotic leak pressure)
Olson *et al*[13]	2012	11 intern	Open laparotomy and bowel anastomosis	OSATS and survey

OSATS: Objective Structured Assessment of Technical Skills; ROVIMAS: RObotics VIdeo and Motion Assessment Software; GRS: Global Rating Score; FPA: Final product analysis.

remained that dealt with technical skills assessment in general surgery. These selected articles were divided into 4 categories according to the skills assessed; open skills (Table 1), laparoscopic skill (Table 2), combination of open and laparoscopic skills (Table 3), and endoscopic skills (Table 4). Out of these articles only 12 studies integrated simulators in a surgical curriculum with technical skills being assessed (Table 5). Only 1 study was found using simulators in the selection process into surgical training programme.

With an increasing emphasis of surgical procedures being undertaken in a minimally invasive approach, it is not unsurprising that the assessment of laparoscopic skills dominate the articles included. This bias is also a result of the reality that laparoscopic skills assessment in a simulator has proved far easier than the assessment of open surgical skills. However, observational-type assessment tools remain the instrument of choice in all the skills, especially when assessing trainees in a real operating theatre (OR).

In the studies identified, 21 employed observational tools, mainly Objective Structured Assessment of Technical Skills (OSATS) as the main scoring system to evaluate their candidates' technical skills performances in open and laparoscopic skills.

The use of simulators in the assessment of laparoscopic skills was evident in 23 publications. Nineteen studies utilised the objective metrics generated by the simulator only and 3 studies used FLS scoring system. One study[17] combined the objective metrics from the simulator with error or injury scores. A total of 13 studies that assessed laparoscopic skills in simulators were using OSATS or checklist-based tools, solely. Out of these, 2 studies[43,45] assessed trainees in the operating theatre (OR) using video-based observational tools following simulation-based training. Interestingly one study[39] combined the performance score on simulator with performance in the OR. Five studies[14,36,37,48,50] used ICSAD combined with other assessment tools or simulator-generated metrics in both open and laparoscopy.

Table 5 outlines reports that incorporated simulators as part of the course in their curriculum. Two of them were for open surgical skills, 6 studies were for laparoscopic skills, 3 studies were for both open and laparoscopic skills and only 1 for endoscopic skills assessment.

One study[40] used virtual reality laparoscopy simulator to assess general surgical applicants who were shortlisted for the residency interview. However, the scores were not used in ranking the candidates for acceptance into the training programme.

DISCUSSION

Simulation in surgery has been a hot topic among surgical educators for more than a decade. In the early millennium, there was an avalanche of studies using simulators that focused on validating the simulators and proving their reliability and fidelity. Since the year 2000 approximately 173 studies were published that specifically reported construct validity of a wide spectrum of surgical simulators. Many new technologies evolved to progressively improve the existing simulators to higher fidelity systems. However despite the plethora of validation studies being completed over a decade ago there is a glaring hiatus in the literature when one examines the results of the integration of these simulators into surgical training curricula. In particular, there is a lack of study showing the implementation of these simulators in the surgical training institutions across the globe, especially in the arena of surgical skills assessment for credentialing. From our review only 12 studies could be identified from the five hundred triaged that have integrated simulation into a surgical training curriculum. There were 52 studies that used simulators in surgical skills assessment within general surgery. The size of these studies was quite modest with 34 having less than 40 candidates and only 5 having greater than 100 candidates.

The main purpose of having simulators in the surgical training arena is for the acquisition of technical skills appropriate to the level of training. This may be undertaken in a safe training environment both from the trainees and patients' viewpoint. Simulation-based surgical training is important in teaching the surgical trainees and to monitor their progress along the training programmes until they possess the essential technical skills without risking patients' lives. In order to grasp this, continuous training and assessment is paramount. Traditionally, trainees' surgical skills are being assessed by examining the logbook and supervisor feedback after certain amount of time in the service. However it is clear that a logbook records experience and is not a marker of expertise[61]. It contains the number of procedures and supervision code, rather than

Table 2 Study characteristics of studies assessing laparoscopic skills (n = 37)

Ref.	Year	No. of participants	Tasks	Assessment tool
Aggarwal *et al*[14]	2007	20 trainees	Laparoscopic cholecystectomy	Motion analysis and video-based GRS
Arora *et al*[15]	2011	25 surgeons	Laparoscopic cholecystectomy	OSATS
Bennett *et al*[16]	2011	70 students	Camera navigation	Box trainer
Botden *et al*[17]	2009	18 students	Laparoscopic suturing	ProMIS™, FPA using 5-point Likert Scale
Buzink *et al*[18]	2012	25 trainees 6 experts	Diagnostic laparoscopy, laparoscopic cholecystectomy and laparoscopic appendicectomy	LapMentor
Cope *et al*[19]	2008	22 interns	6 tasks on MIST VR	MIST VR
Crochet *et al*[20]	2011	26 trainees	Laparoscopic cholecystectomy	VR Simulator
Ganai *et al*[21]	2007	19 students	Angled telescope navigation	VR Simulator
Grantchar-ov *et al*[22]	2009	37 residents	Basic laparoscopic task	MIST VR
Heinrich *et al*[23]	2007	17 experts	26 modules	LapMentor, LapSim, ProMIS™, Surgical SIM
Kanumuri *et al*[24]	2008	16 students	Laparoscopic suturing and knot tying	Video-based performance assessment tool on live porcine
Kolozsvari *et al*[25]	2012	63 residents	FLS tasks[1]	FLS scoring system
Kurashima *et al*[26]	2013	17 residents	Laparoscopic inguinal hernia repair	GOALS-GH
Langelotz *et al*[27]	2005	150 surgeons	Navigation, coordination, grasping, cutting and clipping	VR simulators
LeBlanc *et al*[28]	2010	29 surgeons	Laparoscopic sigmoid colectomy	ProMIS™ simulator, OSATS and operative error
Lehmann *et al*[29]	2012	36 surgeons	2 LapSim tasks	LapSim
Lehmann *et al*[30]	2013	105 surgeons	Lifting and Grasping, Fine dissection	LapSim
Loukas *et al*[31]	2011	25 trainees	Adhesiolysis, bowel suturing, laparoscopic cholecystectomy	LapVR
Loukas *et al*[32]	2011	20 trainees	Adhesiolysis, bowel suturing, laparoscopic cholecystectomy	LapVR
Loukas *et al*[33]	2012	44 novices	Peg transfer, cutting, knot tying	LapVR and video trainer
Lucas *et al*[34]	2008	32 students	Laparoscopic cholecystectomy	OSATS
Mansour *et al*[35]	2012	48 trainees	Peg transfer, clipping	VR simulators
Munz *et al*[36]	2007	20 novices	Intracorporeal knot tying	ICSAD and checklist
Munz *et al*[37]	2004	24 novices	Cutting a shape on a glove and clipping a rubber tube	Motion analysis and error score
Palter *et al*[38]	2012	25 residents	Laparoscopic right colectomy (live and simulator)	Video-based procedure-specific evaluation tool, modified OSATS global rating scale and LapSim
Palter *et al*[39]	2013	20 trainees	Clipping, and lifting and grasping, laparoscopic cholecystectomy (actual OR)	Video-based procedure-specific evaluation tool, modified OSATS global rating scale and LapSim
Panait *et al*[40]	2011	42 applicants	Navigation, coordination, grasping, cutting and clipping	LapSim
Rinewalt *et al*[41]	2012	20 residents	FLS tasks	GOALS
Rosenthal *et al*[42]	2006	20 students	Clip and cut cystic duct	Xitact LS500 Virtual Patient
Seymour *et al*[43]	2002	16 trainees	Laparoscopic cholecystectomy (OR)	Video-based operative error scoring system
Sharma *et al*[44]	2013	19 trainees	Laparoscopic cholecystectomy	LAP MentorTM
Stefanidis *et al*[45]	2013	42 novices	Laparoscopic suturing (OR)	GOALS, speed, accuracy and inadvertent injuries
Stelzer *et al*[46]	2009	23 interns	Peg transfer, intracorporeal knot tying in dry lab, running the bowel, intracorporeal knot tying in live porcine model	MISTELS scoring system Video-based modified GOALS
Tanoue *et al*[47]	2010	194 surgeons	Lifting and grasping	LapSim
Torkington *et al*[48]	2001	13 trainees	MIST VR tasks	ICSAD and MIST VR
van Rijssen *et al*[49]	2012	162 trainees	Intracorporeal knot tying	OSATS and Motion Analysis Parameter (MAP)
Varas *et al*[50]	2012	25 residents	Laparoscopic jejunojejunostomy	OSATS, ICSAD, FPA

[1]FLS tasks are peg transfer, pattern cut, endoloop placement, suture with an extracorporeal knot and suture with an intracorporeal knot. GRS: Global rating scale; OSATS: Objective Structured Assessment of Technical Skills; FPA: Final product analysis; MIST-VR: Minimally invasive surgical trainer-virtual reality; VR: Virtual reality; FLS: Fundamentals of laparoscopic surgery; GOALS: Global operative assessment of laparoscopic skills; GOALS-GH: Global Operative Assessment of Laparoscopic Skills-Groin Hernia; OR: Operating theatre; MISTELS: The McGill Inanimate System for Training and Evaluation of Laparoscopic Skills; ICSAD: Imperial College Surgical Assessment Device.

performance scores for a particular procedure. Therefore, logbooks lack content validity[62]. Supervisor feedback assesses the overall performance of a particular trainee and is not exclusively on the technical skills. It is largely subjective and influenced by multiple factors such as patients' condition, theatre environment and hospital condition. Therefore, the need for a more robust assessment tool which is objective, reliable and feasible[63] remains.

In our institution surgical simulators are used as part of the initial selection process and thereafter for skills assessment and ongoing training. Irish surgical trainees are required to attend simulation-based operative skills classes throughout their training programme. Apart from the didactic teachings, practical sessions are provided which

Table 3 Study characteristics of studies in assessment of open and laparoscopic skills (*n* = 4)

Ref.	Year	Number of participants	Tasks	Assessment tool
Beard *et al*[51]	2011	85 trainees	Mixed tasks (OR)	Procedure-based assessment, OSATS
Fernandez *et al*[52]	2012	30 PGY 1	Knot-tying, suturing, laparoscopic skills	OSATS, computer metric-based performance assessments
Mittal *et al*[53]	2012	60 residents	Basic skills(knot tying,wound closure, enterotomy,vascular anastomosis) and FLS	OSATS and FLS
Parent *et al*[54]	2010	28 interns	Wound closure and FLS tasks	Essential item checklist, economy of time, global competence, FLS system

OR: Operating theatre; OSATS: Objective Structured assessment of technical skills; FLS: Fundamentals of laparoscopic surgery.

Table 4 Characteristics of studies in assessment of endoscopic skills (*n* = 6)

Ref.	Year	Number of participants	Tasks	Assessment tool
Ende *et al*[55]	2012	28 residents	OGD	Simulator and observation
Götzberger *et al*[56]	2011	13 trainees	No mention in abstract	Simulator (5-point Likert scale)
Haycock *et al*[57]	2010	36 trainees	Colonoscopy (simulator and OR)	Direct Observation of Procedural Skills and Global Scores sheet
Haycock *et al*[58]	2009	28 trainees	Polypectomy, control of upper GI bleeding and oesophageal dilation and PEG insertion	Station-specific checklist and global score
Shirai *et al*[59]	2008	20 residents	OGD	11 items 5-grade scale
Van Sickle *et al*[60]	2011	41 trainees	Colonoscopy	GI Mentor Ⅱ and GAGES

OGD: Oesophago-gastro-duodenoscopy; GI: Gastrointestinal; PEG: Percutaneous Endoscopic Gastroscopy; GAGES: Global Assessment of Gastrointestinal Endoscopic Skills.

allow the trainees to practice their skills in open surgery, laparoscopy and endoscopy. Basic surgical trainees are assessed at the end of their training years. Trainees who underperform are required to attend a remedial day where their performances will be discussed with the faculty. For the past 6 years, all candidates shortlisted for Higher Surgical Training (HST) programme in general surgery, cardiothoracic and plastic surgery are required to go through surgical skills assessments prior to their interviews. Their scores carry 10% marks in their overall markings. Gallagher *et al*[64] showed that four out of five top performers on technical skills stations during selection of higher surgical trainee in general surgery were in the top-ranked applicants overall and subsequently succeeded in being selected into the HST programme. In plastic surgery, Carroll *et al*[65] proved those applicants selected for HST performed better in all six tasks (laceration repair, Z-plasty, lipoma excision, sebaceous cyst excision, tendon repair and arterial anastomosis) than those who were not.

OSATS remains the selected assessment tool of choice in the evaluation of surgical skills. In our own training programme it is used for all open surgical procedures with inanimate bench models such as bowel anastomosis, excision of lipoma or sebaceous cyst and laparotomy incision and closure. Each station is assessed by an expert surgeon relative to the specialty and all stations are run simultaneously within a time frame. For laparoscopic skills, OSATS assessment is combined with performance on ProMIS™ laparoscopic simulator (Haptica, Dublin, Ireland). The tasks for laparoscopic skills generally include object positioning and sharp dissection. Promis™ simulators score the trainees or candidates according to the total path length, smoothness, time and error. In general surgery and cardiothoracic skills assessment, the GI Mentor endoscopy simulator (Simbionix, Cleveland, OH, United States) and a 15-item checklist are used to assess candidates' endoscopic skills. GI Mentor could provide time and the percentage of mucosa visualised as objective score in the assessment.

From this review, we identified that the main instruments utilised in practice remain observational tools for both open and laparoscopy. This is despite a myriad of validated computer-based simulators being available in laparoscopy. The most commonly used observational tool is the Objective Structured Assessment of Technical Skills or OSATS. It consists of 2 sets of evaluation checklist; operation-specific checklist and global rating scales. It is consistent with the format of the typical Objective Structured Clinical Examination (OSCE) in which examinees perform a series of clinical tasks at each of several time-limited stations[66]. In another study[41], a different type of observer-dependant assessment tool was used for assessing laparoscopic skills called Global Operative Assessment of Laparoscopic Skills (GOALS). It was developed by a group of researchers[67] in Quebec, Canada. This consists of a checklist and 2 visual analogue scales (VAS). All these observational tools require a minimum of two independent assessors in order to avoid bias in scoring the candidates by single assessor. Therefore, a group of expert surgeons should be recruited to use these assessment tools. This could be done either live during the assessment or by video recordings. Since

Table 5 Characteristics of studies integrating skills assessment tools in a simulation-based curricula and selection process (n = 12)

Ref.	Year	No. of participants	Tasks	Assessment tool
Open skills				
Chipman *et al*[11]	2009	24 trainees	Excision of skin lesion and wound closure	OSATS
Olson *et al*[13]	2012	11 interns	Open laparotomy, bowel anastomosis	OSATS and survey
Laparoscopic skills				
Buzink *et al*[18]	2012	25 trainees 6 experts	Diagnostic laparoscopy, laparoscopic cholecystectomy and laparoscopic appendicectomy	LapMentor
Palter *et al*[39]	2013	20 trainees	Clipping, and lifting and grasping, Laparoscopic cholecystectomy (actual OR)	Video-based procedure-specific evaluation tool, modified OSATS global rating scale and LapSim tasks
Panait *et al*[40]	2011	42 applicants	Navigation, coordination, grasping, cutting and clipping	LapSim
Rinewalt *et al*[41]	2012	20 residents	FLS tasks	GOALS
van Rijssen *et al*[49]	2012	162 trainees	Intracorporeal knot tying	OSATS and Motion Analysis Parameter(MAP)
Varas *et al*[50]	2012	25 residents	Laparoscopic jejunojejunostomy	OSATS, ICSAD, FPA
Open and laparoscopic skills				
Fernandez *et al*[52]	2012	30 PGY 1	Knot-tying, suturing, laparoscopic skills	OSATS, computer metric-based performance assessments
Mittal *et al*[53]	2012	60 residents	Basic skills(knot tying,wound closure, enterotomy, vascular anastomosis), FLS tasks[1]	OSATS and FLS score
Parent *et al*[54]	2010	28 interns	Wound closure, FLS tasks[1]	essential item checklist, economy of time, global competence, FLS score
Endoscopic skills				
Van Sickle *et al*[60]	2011	41 trainees	Colonoscopy	GI Mentor Ⅱ and GAGES

[1]FLS tasks are peg transfer, pattern cut, endoloop placement, suture with an extracorporeal knot and suture with an intracorporeal knot. OSATS: Objective Structured Assessment of Technical Skills; FLS: Fundamentals of Laparoscopic Surgery; GOALS: Global Operative Assessment of Laparoscopic Skills; ICSAD: Imperial College Surgical Assessment Device; FPA: Final Product Analysis.

multiple assessors are required to make these tools valuable, there should be a minimum discrepancy between the scores among the assessors. Otherwise, the scores can be open to critique. In order to prove the degree of agreement among the assessors, inter-rater (IR) reliability is used. IR value should be at 0.8, which means the assessors are in agreement in 80% of the scores but in disagreement in the rest of 20%. A high value of IR reliability indicates that the scores are homogenous and the assessment tool is both robust and of value. In one of the study[13], IR reliability was 0.67 which reflects significant differences of opinion of assessors in the subjective data they are evaluating. This emphasises the weakness of this scoring system, as well as the labour intensive nature of the scoring system. In all these studies the candidates could feel appropriately aggrieved if the arbitrators of success in any task undertaken demonstrated significant difference in opinion as evidenced by such a low IR reliability score. We would contend that the use of a truly objective assessment *via* simulation in real time must inherently be a stronger approach to assessment.

As with every technology there are a variety of simulators available on the market that has been used in surgical skills assessment. In laparoscopic training and assessment, computer-based simulators are able to provide objective metrics after completion of a laparoscopic task. Some examples of validated virtual reality (VR) simulators available in laparoscopy are MIST VR, LapSim, LapMentor and Xitact LS500[68]. These simulators are able to assess various laparoscopic skills such as camera navigation, object positioning and manipulation, intracorporeal suturing and sharp dissection. However, the main criticism on VR simulators is that they lack of real life representation such as delayed gravity effect and no haptic feedback, as found in LapSim[36].

A hybrid simulator, ProMIS^{TM} (Haptica, Dublin) used 100% VR for certain tasks and augmented reality that overlays graphics onto a task performed on a physical exercise[69]. It provided the tactile feedback which is lacking in most VR simulators. VR and hybrid simulators are able to quantify skills in terms of path length, smoothness, economy of movement and time. The simulators also are able to identify the errors performed specific to the procedures and include them in the final report. Various studies have shown their validity and reliability[70-76]. However, these simulators are largely used for learning and practising the skills but rarely used as an assessment tool. Only 56% of the studies in this review employed simulator-generated objective metrics in the laparoscopic skills assessment, either exclusively or combined with other assessment tools.

Endoscopic skills also can be trained and assessed using simulators. Training in endoscopy in a virtual environment is thought to be a good alternative to classical bedside teaching, but without its adverse effects, such as patient discomfort, risk of perforation, and longer examination time[77]. GI Mentor (Symbionix, Israel) is one of the commonest endoscopy simulators used in surgical training institution. After the performance of a case on the simulator, the trainee is presented with an evaluation of performance such as time taken, percentage of mucosa visualized, and percentage of time spent without

clear vision (red-out)[78]. Recently, Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) developed Fundamental of Endoscopic Surgery™ (FES™) as a training and assessment tool for basic skills in endoscopy[79].

There are fundamental differences in the skills required for laparoscopic surgery as compared to open surgery[80]. Without doubt it is clear from the literature that the use of simulators in open surgery represents a challenge. In general the progression of simulator development has tended to target minimally invasive surgery (MIS)[75]. Nonetheless, open surgery remains to be the paramount procedures across surgical specialties. It is vital to teach surgical trainees and assess their skills in open surgery during their training years. Inanimate bench models such as the laparotomy model from Simulab Corporation (Seattle, WA), skin pads and saphenofemoral junction model from Limbs and Things (Bristol, United Kingdom) are amongst most commonly used in training and assessment. Animal models, either cadaveric or live, have been used in some studies but plagued by ethical issues in regards to animal rights. In United Kingdom, the use of live animals is not permitted under the current law, unlike in Europe, United States and other countries[81]. Martin *et al*[82] showed bench top simulations gave equivalent results to the use of live animals.

The challenge for the assessment of open surgical skills is to decide what parameters should be evaluated. The role of simulators in the assessment of open surgery however may lie in the determination of a surgeon's dexterity. The objective measurement of a surgeon's technical skill or level of dexterity has proved to be very difficult. Surprisingly only 1 study combined OSATS with motion analysis system in an attempt to capture the essence of dexterity[10]. The technology behind the measurement of dexterity in surgery and in particular open surgery is however slowly evolving. The researchers in Imperial College London developed a motion tracking system called Imperial College Surgical Assessment Device (ICSAD). This is a combination of a commercially available electromagnetic tracking system (Isotrak Ⅱ, Polhemus Inc,Colchester, VT) and bespoke computer software program[83]. It measures the time taken, path length and number of movements in open and laparoscopy skills assessment. This has been shown that the measurements were able to discriminate different level of surgical experience in laparoscopy[48] and open surgical procedures[84]. Then, RObotics VIdeo and Motion Assessment Software (ROVIMAS) replaced the former ICSAD motion analysis software and integrated an improved version of data acquisition module including real-time synchronized motion-video capture functionality[85]. Despite these technologies being now over a decade old it remains largely a research tool rather than incorporated into main stream curricula.

The measurement of dexterity alone is insufficient without it being in the appropriate context. In essence, dexterity may be independent of the quality of the end result: This represents surgical context. Errors such as slip knot and incorrect suture placement could cause horrendous morbidity towards patients. It is the appreciation of these errors that underpins the concept of placing skills assessment and the associated metrics in the correct context.

The majority of assessing errors or analysing the end product is observational. A crude assessment of the quality of the final product is by using a 5-point scale[86]. Scott *et al*[87] formulated a proficiency score which include a series of errors observed for knot tying and suturing skills and maximum allowable task duration as cutoff time. The formula used was as follow: Score = (cutoff time) - (completion time) - 10 (sum of errors); a higher score indicates superior performance[86]. A significant weight was given to the sum of errors showing the importance of the end-product quality in surgical skills assessment. Patel *et al*[88] developed low-fidelity exercises for basic skills training and assessment and proved its validity. The exercises were needle driving, knot tying, two-hand coordination and fine motor coordination. The metrics measured include time, accuracy and number of targets completed for needle driving exercise or number of appropriate knots for knot tying exercise. Again, this is open to bias and labour intensive. In practice, the quality of knots is easily tested by spreading the loop until they are either break or slip. However, this is hardly performed with a standardised force by surgical educators. Several studies have used tensiometers to assess the quality of the knots[89-92]. Brydges *et al*[93] developed a measurement for wound closure skill performance called 'absolute symmetry error', which measure related to the "bite size" on each suture placement. It does not require an expert assessor and feasible for self-training and assessment. A few studies assessed the end product of bowel anastomosis by measuring the leak pressure[12,50]. These studies combined the validated assessment tool with final product analysis (FPA). By combining these components in the assessment of skills, trainees' appraisal is thought to be more accurate and apparent. From our review of the literature, only 2 studies[17,28] combined virtual reality simulator generating metrics combined with error scoring systems in their assessments. This approach would seem sensible when one is considering surgical skills assessment.

There is a vast quantity of published data available underpinning the validity of surgical simulators. However, it was abundantly evident from our review that only a small number of papers have outlined their use as part of a training curriculum. It should be noted that the literature search was restricted to English language publications only. In total, twelve studies were identified that incorporated simulation-based training in the curriculum. The participants in these studies went through various periods of time in training using simulators and their performances in technical skills were assessed at the end of the training phase. OSATS or other observational tools were used to assess open skills in 5 studies. For

laparoscopic skills, only 2 of these articles used simulators alone in the assessment and 3 studies combined the simulator score with observational assessment tools. Only 1 study[50] assessed trainees' performances using multimodal assessment tools which were OSATS, ICSAD and final product analysis (FPA) (leakage and permeability of an anastomosis). In another study[60], endoscopic skills were assessed by a combination of the simulator-based scores and Global Assessment of Gastrointestinal Endoscopic Skills (GAGES) scores. Two studies developed intensive boot camp session for new residents in order to boost their basic technical skills at the start of their training programme[52,54]. Both studies assessed open technical skills using observational tools and for laparoscopic skills, one study[52] used computer-generated metrics and the other study[54] used FLS scoring system. Fernandez *et al*[52] proved that the new residents' performances improved after the 9-wk intensive course. However, in the other study[54] the boot camp course ran for only 3 d and the performances did not show any significant difference compared to the control group. Interestingly, only 1 study[38] assessed trainees performances in a simulation lab and thereafter in OR. After training to proficiency with the simulators, the trainees were required to perform laparoscopic cholecystectomy with their supervisors and the performances were video-recorded. These recordings were then assessed using observational tools. This was the only study that seemed to report active integration of simulator based surgical skill training and translation into real time clinical practice.

It is clear that the assessment of surgical skills in simulation laboratories is robust. The critical question is whether the skills acquired from simulation-based curriculum are transferrable to real operations. The most recent systematic review by Buckley *et al*[94] demonstrated that simulation-based training has a positive impact on operative time and predefined performance scores in the OR but not the quantifiable measures such as ergonomics, hand dominance and smoothness of movement as measured by simulators. The fundamental assumption of simulation-based training is that the skills acquired in simulated settings are directly transferable to the operative setting[95]. If this assumption is proven to be true, simulation-based curriculum must be one of the main pillars in creating top-quality surgeons which in turn would guarantee an excellent patient care and safety.

Over the last decade, observational assessment tools, such as OSATS, remain the most used methodology to assess surgical skills. It has been over a decade since motion tracking systems were reported as effective tracking tools in assessing surgical skills[96]. Despite the advancement in simulation technology, this available technology has not been fully incorporated into surgical training curricula. This is particularly true for the assessment of open skills. One must therefore query why this is the case. We initially had a frenzy of validation studies since the turn of the millennium in relation to simulators. Following this, technology has only improved in terms of fidelity and reproducibility. The dearth of information in the literature regarding the efficacy of the use of simulators in training programmes may be related to the paucity of data on translating simulator based training into the real patient setting. Yet the conversion from VR to OR as coined by Professor Anthony Gallagher[97] perhaps is finally beginning to get traction. In the past 14 years there have been 12 articles that report their experience of simulators within their general surgical training programmes. One of these has now translated this VR training into OR in practice.

The integration of surgical skills assessment as part of the selection process for Higher Surgical Training (HST) selection in the Irish National Training Programme is a further example of the potential that simulation holds for the surgical training community. One can only hope that over the next decade, now that the validity of simulator based training has finally being accepted, the future of simulation-based surgical training will no longer stand on the precipice but finally take flight.

COMMENTS

Background

The traditional apprenticeship model for surgical training as described by William Halstead is reliant on opportunity in order to gain sufficient surgical skills. In the current climate, surgical training is focusing on integrating simulators in the formal curricula, including surgical skills assessment of the trainees.

Research frontiers

For the past 14 years, there is a plethora of published studies that involved validation of various simulators. However, the integration of these simulators in surgical skills assessment as an objective measurement is still minimal.

Innovations and breakthroughs

The authors identified that observer-dependant tool remains largely a tool of choice when assessing both laparoscopy and open technical skills. Some of the studies outlined the use of simulators in objective assessment of laparoscopic skills and minimum amount of studies showed the application of non-observer dependant tool in the assessment of endoscopic and open surgical skills.

Applications

The assessment of surgical skills using simulators is highly applicable in surgical curriculum. The next step is to engage the simulation technology in the assessment of technical skills in a real operative setting.

Terminology

Observational tool: Checklist-based assessment tool used by surgical experts; OSATS: Objective Structured Assessment of Technical Skills.

Peer review

This is a very nice review of the available literature on the results of simulation training on surgical residents.

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CASE REPORT

Cyanoacrylate spray as treatment in difficult-to-manage gastrointestinal bleeding

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Abstract

Gastrointestinal bleeding can be a life-treating event that is managed with standard endoscopic therapy in the majority of cases. However, up to 5%-10% of patients may have persistent bleeding that does not respond to conventional measures. Several endoscopic treatment techniques have been proposed as strategies to control such cases, such as epinephrine injection, hemoclips or argon plasma coagulation, but there are certain clinical scenarios where it is difficult to achieve hemostasis even though adequate use of the available resources is made. Reasons for these failures can be associated with the lesion features, such as extent or location. The use of long-standing techniques in non-traditional scenarios, such as with cyanoacrylate for gastric varices sclerosis, has been reported with favorable results. Although new products such as TC-325 or Ankaferd Blood Stopper hemosprays may be useful, their formulations are not available worldwide. Here we present two clinical cases with very different scenarios of gastrointestinal bleeding, where the use of cyanoacrylate in spray had favorable results in uncommon indications. Cyanoacrylate used as a spray is a technique that can be used as an alternative method in emergent settings.

Key words: Cyanoacrylate; Gastrointestinal bleeding; Hemostasis; Mexico; Spray

Core tip: Up to 5%-10% of patients with gastrointestinal bleeding may have persistent bleeding that does not respond to endoscopic measures. When failure of the initial management strategy is observed, new techniques can be used. Cyanoacrylate is a polymer that crystallizes upon contact with blood and, if used as a spray, can help achieve hemostasis with minimal or no risk to patients.

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INTRODUCTION

Upper gastrointestinal (GI) bleeding is a common disease, with approximately 48% of cases related to peptic ulcer disease[1]. Although endoscopy is highly effective in the control of active bleeding, up to 5%-10% of patients may have persistent bleeding that does not respond to conventional measures, or have recurrent bleeding that is common in conditions in which the underlying disease is not cured (*e.g.*, varices, tumors)[2]. In this scenario, recurrent bleeding can be considered an independent risk factor potentially leading to mortality[1].

An ideal method of endoscopic hemostasis would

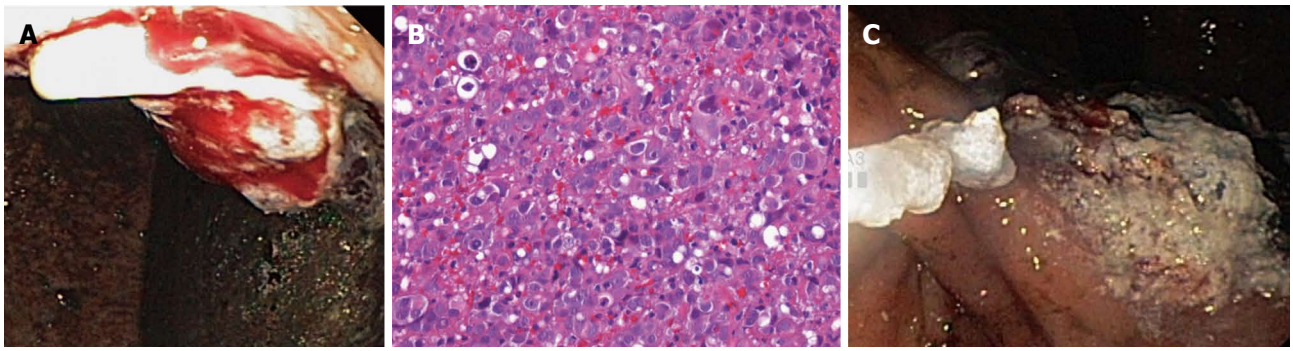

Figure 1 Patient with ulcerated adenocarcinoma of the lower third of the esophagus. A: Ulcerative lesion at the minor curvature with oozing; B: Diffuse adenocarcinoma (poorly differentiated). Neoplastic cells alternate with polymorphonuclear cells; C: Ulcerative lesion after cyanoacrylate spray.

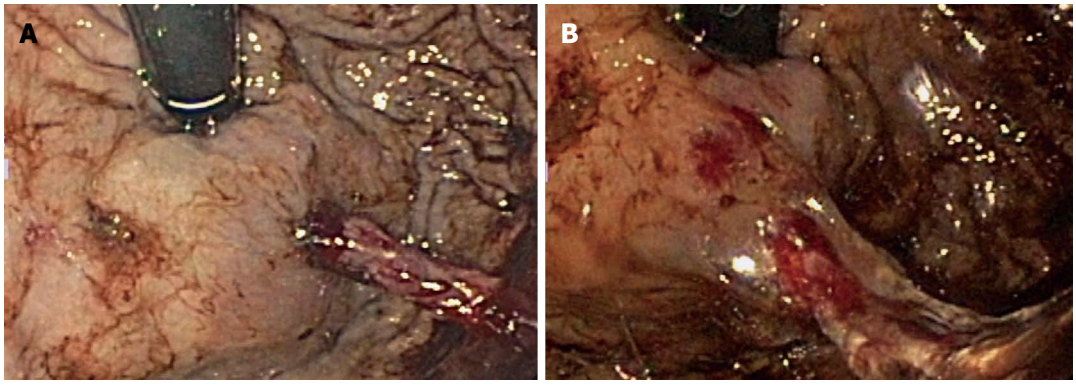

Figure 2 Gastric varices with active bleeding after sclerotherapy with 2-octyl cyanoacrylate. A: Bleeding fundic varices; B: Control of bleeding after placement of cyanoacrylate spray.

immediately stop active bleeding and prevent recurrent bleeding in both the short- and long-term for all types of lesions, be easy to apply to focal and diffuse areas in all locations in the GI tract, cause no significant tissue injury, be safe for the patient, endoscopist, and endoscope, have no limitation regarding the amount of therapy that can be applied, work in patients with decreased thrombotic function, and be inexpensive[3]. Currently, no endoscopic therapy achieves all of these characteristics, so new techniques or products must be proposed. Therapeutic measures using cyanoacrylate spray or new formulations, such as dust Hemospray (Cook Medical, Bloomington, IN, United States) have been proposed to achieve hemostasis[4], but the latter is not available worldwide.

We report two clinical cases and their follow-ups demonstrating the usefulness of cyanoacrylate as a spray for GI bleeding.

CASE REPORT

Patients were seen between October 2013 and January 2014 because of GI bleeding and failure of conventional endoscopic techniques. The clinical courses before and after endoscopies were reviewed. Hemostasis was defined as no oozing or spurting at the conclusion of endoscopy. All patients signed a consent form before the procedures.

Spray technique

Using a 23-gauge injection needle catheter positioned 1 cm outside the tip of the endoscope, a total of 0.5-2.0 mL of a mixture of *N*-butyl-2-cyanoacrylate (Histoacryl; B. Braun Medical, Bethlehem, PA, United States) with lipiodol (0.5 mL:0.6 cc) was sprayed directly over the bleeding site, followed by a rapid 5-mL normal saline solution flush. After the spray, the needle was withdrawn inside the catheter, and the entire endoscope was removed, with the tip of the catheter sheath projecting outside the endoscope. The tip of the catheter was cleaned externally and removed.

Case 1

A 62-year-old male patient with a history of ulcerated adenocarcinoma of the lower third of the esophagus received preoperative chemotherapy and a partial gastrectomy and esophagectomy (with resection of the middle and lower third). After surgery, radiochemotherapy was administered and he remained under surveillance.

After three years of follow-up, the patient showed disease recurrence and presented with melena and epigastric and midgut pain. Upper endoscopy was performed, and a malignant ulcer was seen in the lesser curvature, starting from the anastomosis until the pre-pyloric area, and the pathology report indicated an adenocarcinoma

Table 1 Patients included in previous reports on cyanoacrylate spray use

Ref.	Sex/age (yr)	Cause of bleeding	Prior therapy	Glue mixture	Glue volume	Treatment (n)	Outcome	Follow-up
Walia *et al*[8]	F, 89	2 cm ulcer in duodenal bulb	20 mL of epinephrine solution (1:10000) + bipolar cautery and hemoclips	n-butyl-2-cyanoacrylate/ normal saline	4 mL	1	Successful hemostasis	No rebleeding
	M, 40	3 cm posterior duodenal bulb ulcer with arterial spurting	Epinephrine injection and hemoclip	n-butyl-2-cyanoacrylate/ normal saline	0.5 mL	1	Hemodynamic parameters stabilized	Prophylactic angiographic embolization
	M, 55	2 cm duodenal bulb ulcer with arterial spurting	4 mL of epinephrine injection and bipolar cautery	n-butyl-2-cyanoacrylate/ normal saline	1 mL	1	Recurrent hematochezia 2 d after procedure	Died 31 d later due to uncontrolled sepsis
	M, 69	Oozing gastric vascular ectasia along the lesser curvature	Argon plasma coagulation and hemoclips	n-butyl-2-cyanoacrylate/ normal saline	1 mL	1	Hemostasis	Recurrent gastrointestinal bleeding 18 d later from vascular ectasia in a different location
	M, 59	Active oozing underneath hemoclip applied after hot snare polypectomy of 1.5 cm rectal polyp	hemoclips	n-butyl-2-cyanoacrylate/ normal saline	0.5 mL	1	Hemostasis achieved	No rebleeding
Prachayakul *et al*[6]	M, 84	5 cm gastric cancer at lesser curvature with oozing	Epinephrine injection (1:20000)	En/Lip 0.5:0.8 + sterile water	3.0 mL	1	Hemostasis achieved	No rebleeding at 9 wk
	F, 76	5 cm sessile polyp in the ascending colon with oozing	Epinephrine injection (1:20000)	En/Lip 0.5:0.8 + sterile water	2.0 mL	1	Hemostasis achieved	No rebleeding at 5 wk, patient died
	M, 15	Metastasizing germinoma with duodenal invasion	Epinephrine injection (1:20000)	En/Lip 0.5:0.8 + sterile water	1.0 mL	1	Rebleeding at 48 h, and required angio-embolization	Continues to bleed, patient alive
	M, 56	Pancreatic cancer with gastric invasion (6 cm ulcerating mass with oozing in the upper part of the lesser curvature)	Metallic clip	En/Lip 0.5:0.8 + sterile water	1.0 mL	1	Hemostasis achieved	No rebleeding at 6 wk
	F, 62	Ampullary carcinoma with invasion to the second portion of duodenum	Epinephrine injection (1:20000) Argon plasma Failed embolization	En/Lip 0.5:0.8 + sterile water	1.5 mL	1	Hemostasis achieved	No rebleeding at 9 wk, patient died
Shida *et al*[7]	-	Pancreatic cancer with invasion into intestinal wall	No data	n-butyl-2-cyanoacrylate/ normal saline	0.5 mL	No data	Hemostasis achieved	No data
	-	Gall bladder cancer with invasion into intestinal wall	No data	n-butyl-2-cyanoacrylate/ normal saline	0.5 mL	No data	Hemostasis achieved	No data
	-	Mucosal resection in sigmoid colon	No data	n-butyl-2-cyanoacrylate/ normal saline	0.5 mL	No data	Hemostasis achieved	No data
	-	Duodenal ulcer	No data	n-butyl-2-cyanoacrylate/ normal saline	0.5 mL	No data	Hemostasis achieved	No data

En/Lip: Enbucrilate/lipidol.

(Figure 1A and B). Further studies confirmed the diagnosis of stage Ⅳ esophageal adenocarcinoma. Fifteen days later, the patient returned due to two episodes of melena, associated with epigastric and mesogastric pain with hemoglobin 10.1 g/dL. In the upper endoscopy, no specific source was detected and oozing was observed in the entire ulcerated area of the lesser curvature. Histoacryl with lipidol (1 mL total) was sprayed on the surface of the tumor through a 23-G catheter until hemostasis was achieved (Figure 1C). The patient was discharged after 72 h with no evidence of rebleeding. After six weeks of follow-up, the patient was alive with no evidence of recurrence of bleeding.

Case 2

A 48-year-old male patient with a history of type 2 diabetes mellitus, hypertension, Evans Syndrome, chronic renal failure, heart failure (American Heart Association/New York Heart Association class Ⅱ-Ⅲ), and decompensated liver cirrhosis due to hepatitis C virus infection (ascites and recurrent variceal bleeding) was admitted for upper endoscopy. Large esophageal varices were observed along with gastric varices (GOV1). Sclerotherapy of gastric varices was performed with 2-octyl cyanoacrylate, but hemostasis was not achieved, with the presence of persistent bleeding after puncture (Figure 2A). Therefore**,** Histoacryl with lipidol was sprayed on the surface through a 23-G catheter until hemostasis was achieved (Figure 2B). In the follow-up, no recurrent bleeding was documented and the patient was discharged after 72 h. After three months of follow-up, no recurrence of bleeding or adverse effects were reported.

DISCUSSION

We demonstrate favorable results with cyanoacrylate spray application in two different cases of difficult-to-treat GI bleeding. Cyanoacrylate has been intensively studied and has been clinically applied as a tissue adhesive in ear surgery, bone grafts, repair of fistulas and skin closures[5]. Cyanoacrylate is from a class of synthetic rubbers that are used as monomers and polymerize in an exothermic reaction after coming into contact with a weak base such as blood[5]. There are two forms used in endoscopy. Enbucrilate (*N*-butyl 2-cyanoacrylate; Histoacryl) is formed of an alkyl group of four carbons, whereas acrylate (2-octyl cyanoacrylate) has an alkyl group of eight carbons (Dermabond; Johnson and Johnson, New Brunswick, NJ, United States)[5]. Histoacryl has been widely used for digestive bleeding due to gastric varices, and is currently medically approved by the United States Food and Drug Administration. It has several advantageous properties, among which the polymerization upon contact with blood enables its effective use. It is thought that the fluid used to clean the injection needle can influence the polymerization time. For the present cases, a saline solution was used for cleaning the needle at the end of the procedure as it triggers polymerization of the rubber, which does not occur with distilled water. We achieved similar favorable results with this combination as with a previous report by Prachayakul *et al*[6].

The use of cyanoacrylate in a spray is not a standard modality for endoscopic treatment of GI bleeding. Table 1 describes the 14 cases that have been reported. Most of the cases used the technique with only saline reported by Shida *et al*[7], which was used as a rescue therapy in lesions where hemostasis had been difficult to achieve by conventional methods with argon plasma, epinephrine or hemoclips[7]. In these cases, hemostasis was achieved, but there were no data on the follow-up of the patients. Prachayakul *et al*[6] reported the successful use of cyanoacrylate and lipidol in a 0.5:0.8 ratio with sterile water with no adverse effects for treating tumoral lesions[6]. Only one of their patients showed rebleeding during the nine-week follow-up period. In the data presented by Walia *et al*[8], three patients experienced rebleeding in a median follow-up of 42 d (range: 30-120 d)[8]. In our two cases, neither of the patients presented recurrence of bleeding on follow-up.

The importance of this technique is the ease of use and the absence of special equipment required, making it accessible to different institutions and clinical settings. We report the use of this technique in two different clinical settings of GI bleeding with favorable results. There has been concern about the possibility of embolism with intravenous application, but this would not occur with the spray technique. There are reports of new products, such as Hemospray and Ankaferd Blood Stopper (Ankaferd Health Products Ltd., Istanbul, Turkey)[9], but these products are not available worldwide.

In conclusion, cyanoacrylate used as a spray is a technique that can be used as an alternative method in emergent settings for uncontrollable GI bleeding.

COMMENTS

Case characteristics

Two patients with persistent gastrointestinal (GI) bleeding that did not respond to conventional measures of endoscopic treatment.

Clinical diagnosis

One patient with gastric varices and another with ulcerated adenocarcinoma of the lower third of the esophagus.

Treatment

Endoscopic treatment with Histoacryl sprayed directly over the bleeding site was used with good results.

Related reports

Scarce information about cyanoacrylate in spray is reported.

Experiences and lessons

Cyanoacrylate used as a spray is a technique that can be used as an alternative method in emergent settings for uncontrollable GI bleeding.

Peer review

The authors describe the technique of using cyanoacrylate spray for GI bleeding and two successful cases are reported. The article provides a technique that is useful in a clinical background.

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CASE REPORT

Endoscopic retrieval of an 18-cm long chopstick embedded for ten months post-automutilation in the esophagus of a patient with psychosis

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Abstract

Foreign body ingestion is an emergency or acute situation that commonly occurs in children or adults and involves the ingestion of one or more objects. Moreover, once the discovery of swallowed foreign bodies has been made, families are typically very anxious to have the patient see a doctor. If the foreign object becomes embedded in the digestive tract, it must be removed; in emergencies, this is done by endoscopy or surgery. This case report presents the successful endoscopic retrieval of a chopstick with both sides embedded 4 cm into the esophageal wall for > 10 mo in a male patient following automutilation in an attempt to be released from a psychiatric hospital. Hot hemostatic forceps were used to open the distal esophageal mucosa in which the chopstick was embedded. The procedure was performed under intravenous general anesthesia and took approximately 7 h.

Key words: Foreign body; Esophagus; Endoscopy; Chopstick; Gastroscope; Hot hemostatic forceps

Core tip: Foreign body ingestion is an emergency that often occurs in children or adults with psychiatric disorders or mental retardation. Here, we report the unique case of a chopstick lodged in the esophagus for 10 mo in a 50-year-old man. The chopstick was embedded 4 cm into the esophageal wall at both ends. Therefore, the procedure was performed under intravenous anesthesia. We made a 4-cm long incision, approximately 1 cm in depth in the esophageal mucosa using hot hemostatic forceps. This procedure took approximately 7 h to perform and an 18-cm long chopstick was removed.

Li SX, Li H, Chen T, Xu MD. Endoscopic retrieval of an 18-cm long chopstick embedded for ten months post-automutilation in the esophagus of a patient with psychosis. *World J Gastrointest Endosc* 2014; 6(9): 453-456 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i9/453.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i9.453

INTRODUCTION

Ingestion of foreign bodies that lodge in the upper gastrointestinal (GI) tract is a common clinical situation. Most of these objects pass through the GI tract spontaneously, but some require emergency endoscopic or surgical removal. Here, we report the first case of a patient with psychosis who had a chopstick lodged in the esophagus with both ends embedded in the esophageal wall for > 10 mo. The patient had a 2-mo history of repeated fever prior to foreign body removal. Ten months previously, the patient experienced a sudden loss of appetite and displayed repetitive behavior of touching his sternum with his hand. The patient's family brought him food daily. He experienced repeated episodes of emesis and fever for 2

mo before the family brought him to the hospital.

CASE REPORT

Foreign body ingestion is a commonly encountered clinical problem and emergency endoscopy case. The patient had swallowed a chopstick following self-mutilation in an attempt to be released from a psychiatric hospital. He refused to say why he would not take fluids daily until his repeated vomiting and fever gradually exacerbated. The family took him to see a doctor in the GI/Internal Medicine Department of our hospital. Chest computed tomography (CT) revealed the tip of an esophageal foreign body as well as a bilateral lung infection (Figure 1A and B). Gastroscopy revealed a chopstick with both ends lodged 4 cm in the esophagus wall (Figure 1C).

The patient's family chose to have the foreign body removed by gastroscopy rather than by a surgical procedure. Initially, a snare was used to tentatively remove the chopstick, however, this attempt failed (Figure 2A). After that, the bagging around the proximal esophageal mucosa was cut 22 cm from the incisors. However, the esophageal mucosa was fixed, and the field of vision was insufficient. Eventually, the esophageal wall was cut and wrapped on the far side of the chopstick using a hook knife. However, because the esophageal wall mucosa was > 1 cm thick, the hook knife was unable to cut properly. We cut the tissue using hot hemostatic forceps (Figure 2B), the distal end of the chopstick was freed (Figure 2C) and then removed by a snare and foreign body clamp. The full length of the removed chopstick was 18 cm (Figure 2D). The procedure was performed under intravenous anesthesia and took approximately 7 h to perform. On postoperative day 1, the patient experienced sustainable chest pain and had a maximum body temperature of 38.5 ℃. The patient's condition gradually improved, and he was discharged on postoperative day 7.

DISCUSSION

Ingestion of foreign bodies is common in clinical practice[1-3]. However, most foreign body ingestion occurs in children between 6 mo and 6 years of age; the rate of foreign body ingestion in adults is lower[4]. In adults, it occurs more commonly in patients with psychiatric disorders, mental retardation, or impairment caused by alcohol. The vast majority of swallowed foreign bodies are found and removed in a timely manner by endoscopy or surgery. This is the first report of ingestion of a foreign body in a patient with psychosis that remained lodged in the esophagus for > 10 mo. Because patients do not like the psychiatric hospital environment, they attempt self-mutilation in order to go home, according to family members. An 18-cm long chopstick is difficult to swallow and would require an external force to enter the esophagus. The distal end of the chopstick may pierce the esophageal mucosa slightly, but cannot pass through the cardia easily. The esophageal peristaltic wave that occurs while eating may move the chopstick tip in close contact with the esophageal mucosa. Reactive hyperplasia that would subsequently occur could embed the chopstick as a foreign body. In this case, hyperplasia of approximately 4 cm × 2 cm in the esophageal mucosa at both ends of the chopstick was noted after 10 mo.

The type of foreign body may determine the complications. Our patient was first examined to determine whether the chopstick had perforated the esophageal wall; this was suspected as the patient had recurrent fever. The CT results were important, and helped us determine that the chopstick perforated only the hyperplastic tissue and not the esophageal wall.

The type of foreign object differs as well. The commonest types of foreign bodies are endoscopically removed in a reliable and safe manner by skilled endoscopists, with a high success rate[5]. Chopstick removal is associated with a high degree of risk; a skilled endoscopist is needed to perform a preoperative assessment and develop a good treatment plan. Esophageal perforation may require surgical management. We believe that endoscopic removal of foreign bodies is best done in the operating room.

In this case, because both ends of the chopstick were tightly embedded in the esophageal wall membrane, we suggested that the foreign body should be removed surgically, but the family insisted on gastroscopy. We found that this would be possible only if one end of the chopstick could be freed. Initially, we needed to determine if this would be the proximal or distal end. The chopstick was exposed at the distal end, approximately 22 cm from the incisors. Only a slight uplift of the esophageal mucosa was visible, and the mucous membrane was not fixed. Initially, we attempted to cut the esophageal wall which was wrapped around the distal end of the chopstick using a hook knife, but because the esophageal wall membrane was approximately 1 cm thick, the hook knife was not sufficient. We then used hot biopsy forceps to make a vertical incision in the mucosa to free the distal end of the chopstick. Considering the difficult nature of this procedure, it took a long time to perform, and there were concerns that the patient may not tolerate the anesthesia well. We decided to perform the procedure under intravenous anesthesia. Another key factor in this decision was cutting the esophageal wall next to the chopstick[6-8].

The ingestion of foreign bodies is one of the most common endoscopic emergencies in China. However, compared to the cases reported in other studies, this is a special case in that the foreign body was a long chopstick and took us approximately 7 h to complete the procedure. In 2013 (Epub in 2012), we reported the endoscopic management of impacted esophageal foreign bodies and the longest one in this cohort was a 5.5 cm fish bone[1]. In the recent report by Zhang *et al*[9], the mean size of esophageal foreign bodies was less than 2 cm and the endoscopic procedure time was approximately 4 min. To date, the case in the present report is the first clinical report of the longest impacted esophageal foreign body

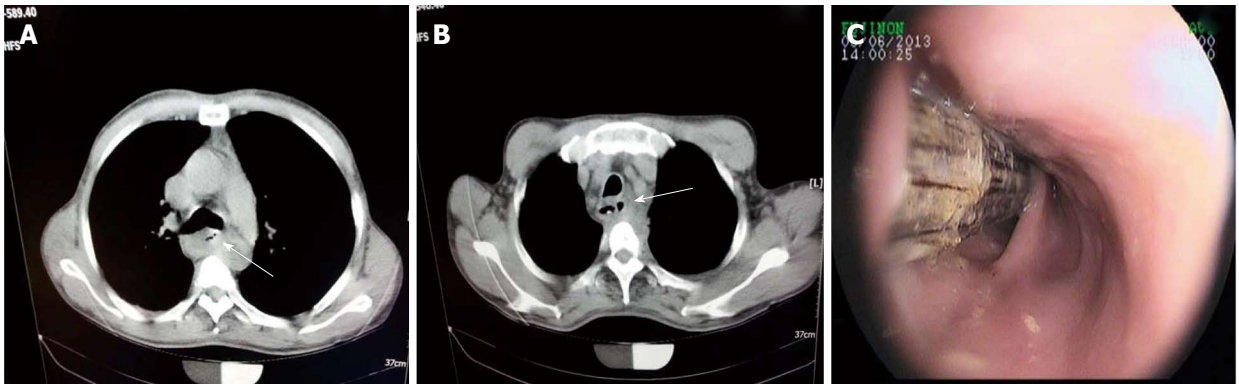

Figure 1 A long chopstick embedded in the esophageal wall. A and B: The roentgenograms showing the foreign body in the esophagus (arrow); C: Endoscopy showing the foreign body in the esophagus.

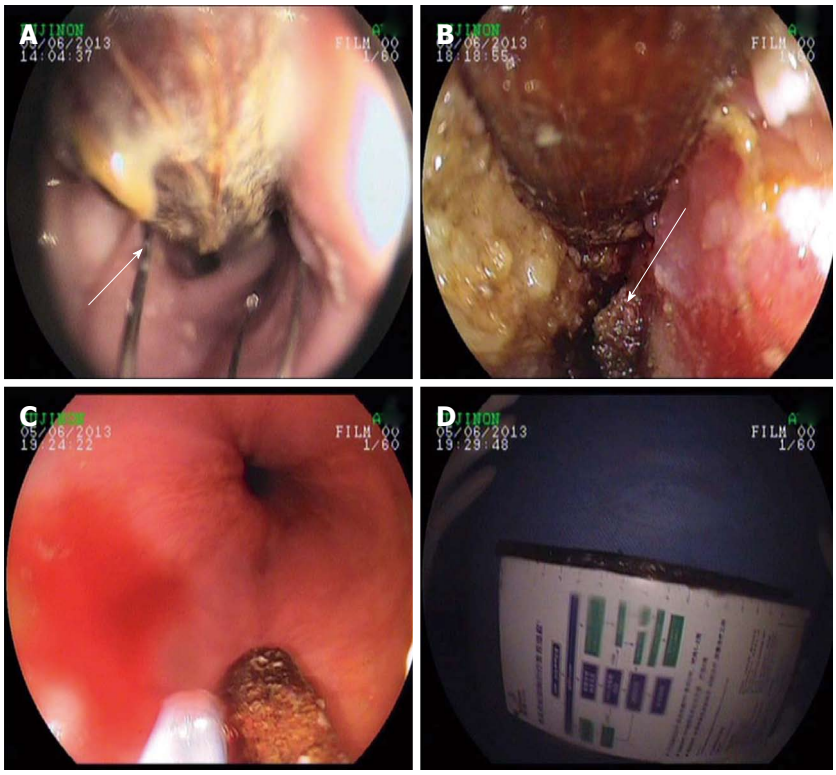

Figure 2 Endoscopic retrieval of the chopstick. A: A snare was tentatively used to remove the chopstick (arrow); B: Hot hemostatic forceps cutting the distal end of the chopstick in the lower esophagus (arrow); C: The freed distal end of the chopstick; D: The 18 cm chopstick measured by a ruler after removal from the esophagus.

removed by endoscopy. Li *et al*[6] stated that when foreign bodies were deeply fixed in the esophageal wall, it was better to avoid any endoscopic attempts and to resort to surgery. However, according to our experience, impacted esophageal foreign bodies can be extracted even when they are fixed in the esophageal wall[1]. Compared to surgery, endoscopic retrieval is minimally invasive and economical, especially in patients older than 60 years, although the procedure time can sometimes be long.

In conclusion, we report our experience of retrieving an 18-cm long chopstick which was lodged 4 cm in the esophageal wall for > 10 mo. To our knowledge, this is the first clinical report of this type of retrieval in a single case.

COMMENTS

Case characteristics

Exacerbated vomiting and fever was described.

Clinical diagnosis

A chest computed tomography (CT) scan revealed the tip of an esophageal foreign body as well as a bilateral lung infection and gastroscopy revealed a chopstick with both ends lodged 4 cm in the esophagus wall.

Differential diagnosis

The gastroscopy confirmed a foreign body in the esophagus.

Laboratory diagnosis

Blood tests were performed routinely and no major clues were found.

Imaging diagnosis

A chest CT scan revealed the tip of an esophageal foreign body.

Treatment

Endoscopic retrieval of the chopstick.

Experiences and lessons

Endoscopy is an effective and minimally invasive treatment for similar cases.

Peer review

This is a very interesting, original case report presenting utility of gastrointestinal endoscopy in diagnosis of psychiatric patient and demonstrating advantage of collaboration between psychiatrists and other clinicians, in management of patients with mental disorders. It is important in face of the fact that this collaboration is very often neglected. This paper is well written and endoscopic procedure is described in detail. The results are clearly presented.

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APPENDIX I-V Instructions to authors

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REVIEW

Risk of transmission of carbapenem-resistant *Enterobacteriaceae* and related "superbugs" during gastrointestinal endoscopy

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Abstract

To evaluate the risk of transmission of carbapenem-resistant *Enterobacteriaceae* (CRE) and their related superbugs during gastrointestinal (GI) endoscopy. Reports of outbreaks linked to GI endoscopes contaminated with different types of infectious agents, including CRE and their related superbugs, were reviewed. Published during the past 30 years, both prior to and since CRE's emergence, these reports were obtained by searching the peer-reviewed medical literature (*via* the United States National Library of Medicine's "MEDLINE" database); the Food and Drug Administration's Manufacturer and User Facility Device Experience database, or "MAUDE"; and the Internet (*via* Google's search engine). This review focused on an outbreak of CRE in 2013 following the GI endoscopic procedure known as endoscopic retrograde cholangiopancreatography, or ERCP, performed at "Hospital X" located in the suburbs of Chicago (IL; United States). Part of the largest outbreak of CRE in United States history, the infection and colonization of 10 and 28 of this hospital's patients, respectively, received considerable media attention and was also investigated by the Centers for Disease Control and Prevention (CDC), which published a report about this outbreak in Morbidity and Mortality Weekly Report (MMWR), in 2014. This report, along with the results of an independent inspection of Hospital X's infection control practices following this CRE outbreak, were also reviewed. While this article focuses primarily on the prevention of transmissions of CRE and their related superbugs in the GI endoscopic setting, some of its discussion and recommendations may also apply to other healthcare settings, to other types of flexible endoscopes, and to other types of transmissible infectious agents. This review found that GI endoscopy is an important risk factor for the transmission of CRE and their related superbugs, having been recently associated with patient morbidity and mortality following ERCP. The CDC reported in MMWR that the type of GI endoscope, known as an ERCP endoscope, that Hospital X used to perform ERCP in 2013 on the 38 patients who became infected or colonized with CRE might be particularly challenging to clean and disinfect, because of the complexity of its physical design. If performed in strict accordance with the endoscope manufacturer's labeling, supplemented as needed with professional organizations' published guidelines, however, current practices for reprocessing GI endoscopes, which include high-level disinfection, are reportedly adequate for the prevention of transmission of CRE and their related superbugs. Several recommendations are provided to prevent CRE transmissions in the healthcare setting. CRE transmissions are not limited to contaminated GI endoscopes and also have been linked to other reusable flexible endoscopic instrumentation, including bronchoscopes and cystoscopes. In conclusion, contaminated GI endoscopes, particularly those used during ERCP, have been causally linked to outbreaks of CRE and their related superbugs, with associated patient morbidity and mortality. Thorough reprocessing of these complex reusable instruments is necessary to prevent disease transmission and ensure patient safety during GI endoscopy. Enhanced training and monitoring of reprocessing staffers to verify the proper cleaning and brushing of GI endoscopes, especially the area around, behind and

near the forceps elevator located at the distal end of the ERCP endoscope, are recommended. If the ERCP endoscope features a narrow and exposed channel that houses a wire connecting the GI endoscope's control head to this forceps elevator, then this channel's complete reprocessing, including its flushing with a detergent using a procedure validated for effectiveness, is also emphasized.

Key words: Endoscopy; Gastrointestinal; Carbapenem-resistant *Enterobacteriaceae*; Cross infection; Disease outbreaks; Healthcare-associated infections; Risk assessment; Disinfection; Sterilization; Anti-bacterial agents; Bacterial infections; Carbapenems; Beta-lactams

Core tip: Gastrointestinal (GI) endoscopy, particularly ERCP, is an emerging risk factor for transmission of carbapenem-resistant *Enterobacteriaceae* (CRE) and their related superbugs, as well as of other certain bacteria and viruses. Several recent reports associate outbreaks of CRE following ERCP, with associated morbidity and mortality. If performed properly, however, current practices for reprocessing GI endoscopes, which include high-level disinfection, appear adequate to prevent disease transmission. Enhancing the quality and safety both of infection control in GI endoscopy departments and of the design of GI endoscopes to facilitate their thorough cleaning and reprocessing is recommended, as it is reasonable to conclude that these recent outbreaks of CRE causally linked to contaminated GI endoscopes may result in more robust and focused oversight and inspections both of manufacturers by regulatory agencies and of healthcare facilities by healthcare accrediting organizations and state health departments. Along with risk assessments, performing root cause analyses that identify the likely causes of CRE outbreaks and the actions required to prevent their recurrence is encouraged.

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INTRODUCTION

Common infection control strategies for the prevention of disease transmission during gastrointestinal (GI) endoscopy are routinely credited for the low reported rate of infections due to a contaminated GI endoscope[1-5]. Bacterial and viral outbreaks following GI endoscopy, with associated morbidity and mortality, have been reported (albeit infrequently) during the past 30 years, but the cause of virtually every one of these outbreaks was attributed to one or more infection control breaches - for example, to: (1) an endoscope reprocessing lapse, including the failure to clean the GI endoscope's instrument channel with a brush; or, the faulty reprocessing of the GI endoscope by an automated endoscope reprocessor, or AER, with a flawed internal design; (2) a damaged or improperly maintained or serviced GI endoscope; or (3) the unsterile administration of an *intravenous* (*iv*) medication[6-14]. Cleaning, high-level disinfection, and drying of the GI endoscope, either in strict accordance with the endoscope's labeling or, alternatively, consistent with any one of a number of recently published endoscope reprocessing guidelines, form the tridental cornerstone of infection control in the GI endoscopic setting.

An outbreak of CRE at "Hospital X" near Chicago (IL) in 2013 following GI endoscopy

Despite GI endoscopy's low reported infection rate, endoscope reprocessing lapses confirmed in recent years have resulted in an heightened focus on patient safety in the GI endoscopic setting[15]. And, with the recent emergence of the "superbug" known as carbapenem-resistant *Enterobacteriaceae*, or "CRE", infection control in this setting has taken on even more urgency and closer examination[16-31]. Much of this enhanced scrutiny in the United States is a direct consequence of the publication in 2014 of a report by the federal Centers for Disease Control and Prevention (CDC) documenting an outbreak of CRE identified the previous year at a hospital located in a suburb of Chicago, IL (United States), known herein as "Hospital X"[25,31]. Part of the largest in United States history, this outbreak of CRE was investigated by the CDC, which determined that 28 and 10 of Hospital X's patients had been colonized and infected, respectively, with a strain of CRE. (With colonization, the patient carries or harbors the bacterium without displaying any clinical symptoms of infection or disease. Infection, in contrast, is associated with the patient eliciting clinical symptoms that meet certain criteria. Colonization can, but does not always, result in infection). According to the CDC, each of these 38 patients was exposed to this superbug while undergoing endoscopic retrograde cholangiopancreatography, or "ERCP", performed by Hospital X between January and September, 2013. (ERCP is a specialized upper GI endoscopic technique that may be used to diagnose and/or treat certain diseases of the biliary or pancreatic ductal systems). The CDC reported its findings in the January 3, 2014, issue of Morbidity and Mortality Weekly Report (MMWR)[25]. The Illinois Department of Public Health and the Cook County Department of Public Health, as well as the Food and Drug Administration (FDA)[25], assisted the CDC with this investigation, a testament to the potentially significant impact of this landmark outbreak of CRE on public health, infection control in the GI endoscopic setting, and the regulation of complex reusable medical instrumentation.

Determining it to be a reservoir of the outbreak's strain of CRE and, therefore, presumably responsible for these 38 patient infections and colonizations, the CDC reported that "the terminal section (the elevator channel)"[25]

of a side-viewing duodenoscope, also known as an ERCP endoscope, which Hospital X used to perform ERCP on several of these 38 exposed patients, was microbiologically sampled and found to be contaminated with both the outbreak's strain of CRE, known as New Delhi metallo-β-lactamase-1 (NDM-1)-producing *Escherichia coli*, and a second strain of CRE[25,31]. Although also cultured from this same ERCP endoscope, however, this second strain, known as *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae*, reportedly did not result in the colonization or infection of any of Hospital X's patients[25]. An ERCP endoscope not related to Hospital X's CRE outbreak is displayed in Figure 1A. Most salient, the CDC reported that this implicated ERCP endoscope remained contaminated with the outbreak's strain of CRE (*i.e.*, NDM-1-producing *E. coli*) despite this instrument (according to the CDC) having been first manually cleaned and then high-level disinfected using an AER. The CDC further reported in MMWR that it did not identify any obvious breaches in the protocol for reprocessing ERCP endoscopes during its investigation of Hospital X's CRE outbreak[25-30].

In this outbreak's aftermath, however, an independent inspection of Hospital X's infection control practices was performed, and a report published, by The Centers for Medicare and Medicaid Services (CMS)[31], which states that the hospital "failed to reprocess ERCP endoscopes as recommended by the endoscope manufacturer"[31]. Namely, according to the CMS's inspection report, the endoscope's manufacturer asserts that Hospital X did not clean the ERCP endoscope using the recommended or approved type of either brush or detergent[31], notwithstanding the CDC's failure to identify any obvious endoscope reprocessing errors[25]. The CMS's inspection report provides three additional facts not reported by the CDC in MMWR: (1) that Hospital X's CRE outbreak in 2013 was associated with the use of not one, but three ERCP endoscopes of the same model type; (2) that at least two of Hospital X's 10 patients infected with the outbreak's strain of CRE died; and (3) that, in addition to the two strains of CRE that the CDC recovered from one of Hospital X's contaminated ERCP endoscope (*i.e.*, NDM-1-producing *E. coli* and KPC-producing *K. pneumoniae*), a third strain of CRE - namely, NDM-producing *K. pneumoniae* - reportedly infected at least one of these two patients who expired (*i.e.*, "Patient #10")[31]. Indeed, Hospital X's CRE outbreak therefore documents a rare instance of patient mortality directly linked to a contaminated GI endoscope. The CDC further reported that the ERCP endoscope's complex physical design "might pose a particular challenge for cleaning and disinfection"[25]. ERCP endoscopes feature a forceps elevator, which is displayed in Figure 1B and is used by the physician during ERCP to manipulate and control the direction and fine movements of accessories that are manually inserted and passed through the GI endoscope's accompanying instrument channel. Figure 1A displays the passage of an accessory through the ERCP endoscope's instrument channel.

Along with the published findings of the CMS's inspection of Hospital X[31], the CDC's contemporaneously published report in MMWR[25] emphasizing that GI endoscopy is an important risk factor for CRE infections and colonizations inextricably introduces concern and confusion about the safety of GI endoscopy vis-à-vis superbug transmissions. (To date, reports of infections of CRE and their related superbugs have been limited to ERCP and esophagogastro-duodenoscopy, or "EGD". While CRE transmissions during colonoscopy would presumably be possible, none has been documented to date). Implying causality, the CDC also reported that once Hospital X replaced the automated high-level disinfection of its ERCP endoscopes with ethylene oxide gas (EtO) sterilization, however, no new cases of CRE transmissions due to a contaminated ERCP endoscope were identified[25,29,31]. Indeed, EtO sterilization is more robust than high-level disinfection performed either manually or using an AER (although EtO sterilization is a more time-consuming process that is no longer used in many healthcare facilities). In addition to some other aspects of its CRE outbreak, however, Hospital X's replacement of automated high-level disinfection, which is a "wet" process requiring that the GI endoscope be subsequently rinsed with (bacteria-free) water following chemical immersion, with EtO sterilization, which conversely is a "dry" low-temperature

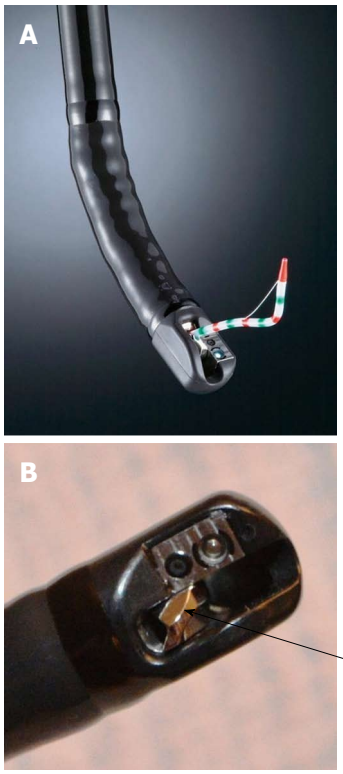

Figure 1 A FujiFilm 530-series duodenoscope and forceps elevator. A: Displayed is a FujiFilm 530-series duodenoscope, also known as an ERCP endoscope. Also displayed is an endoscopic accessory (colored white with green and red strips), which was passed through the endoscope's working (or instrument) channel and is seen exiting the endoscope's distal tip); B: Displayed is the forceps elevator of a FujiFilm duodenoscope. This mechanism is also visible in Figure 1A. [Note: Figures 1A and 1B are reproduced by the permission and courtesy of FUJIFILM Medical Systems U.S.A., Inc. ("FujiFilm"). No correlations or inferences should be made linking FujiFilm products to the transmission of CRE, "superbugs" and/or other related antibiotic-resistant microorganisms that may cause infections].

process that does not use water during any of its stages, to prevent more infections (or colonizations) of CRE might prompt additional speculation about the safety of GI endoscopy and whether current practices for reprocessing GI endoscopes (*i.e.*, high-level disinfection) may not be sufficiently rigorous to prevent transmissions of CRE and other related multidrug-resistant bacteria[26-30].

OBJECTIVE, SCOPE AND METHODOLOGY

This may be both the first and most comprehensive article to evaluate the risk of transmission of CRE and their related superbugs during GI endoscopy. It achieves this objective by providing some background information about *Enterobacteriaceae*, CRE, and β-lactam antibiotics, which include carbapenems to which, as their name indicates, CRE are resistant; by reviewing the recommendations of federal agencies and professional organizations for reprocessing GI endoscopes; and by reviewing, in detail, the CDC's report published in MMWR and the CMS's contemporaneously published hospital inspection report, which both discuss Hospital X's CRE outbreak in 2013 causally linked to contaminated ERCP endoscopes[25,31]. Other instances of disease transmission during GI endoscopy were also reviewed, including several in the FDA's "Manufacturer and User Facility Device Experience" database, or "MAUDE," and in the peer-reviewed medical literature. In addition to outbreaks of CRE and their related superbugs following GI endoscopy, these instances document bacterial (and viral) transmissions *via* contaminated GI endoscopes reported prior to CRE's emergence. While this article focuses primarily on the prevention of transmissions of CRE and their related superbugs in the GI endoscopic setting, some of its discussion and recommendations may also apply to other healthcare settings, to other types of flexible endoscopes, and to other types of transmissible infectious agents. [Note: In the context of this article "related superbugs" are related to, but are not, CRE, *per se*. Specfically, they are gram-negative bacteria that are either: (1) resistant to carbapenem antibiotics, although not of the *Enterobacteriaceae* family (and therefore not CRE; NDM-1 carbapenemase-producing *Acinetobacter baumannii* and *KPC-producing P. aeruginosa* are examples); or (2) are a multidrug-resistant member of the *Enterobacteriaceae* family, although at this time remain susceptible to carbapenem antibiotics (*e.g.*, ESBL-producing *K. pneumoniae*)].

FINDINGS AND RESULTS

GI endoscopes, particularly ERCP endoscopes, pose a risk of transmission of CRE and their related superbugs, both in the United States and globally. Indeed, patient morbidity and mortality due to GI endoscopes contaminated with these antibiotic-resistant bacteria have been documented[13,20-22,24,26-33]. Reports of GI endoscopes transmitting other types of bacteria, too, as well as viruses and other infectious agents, also have been published during the past 30 years. No matter, if performed in strict compliance with the endoscope's labeling, supplemented as needed with professional organizations' published guidelines, however, current practices for reprocessing GI endoscopes, which include high-level disinfection (performed either manually or using an AER), appear sufficient to prevent transmissions of CRE and their related superbugs (provided the high-level disinfectant contacts all of the instrument's contaminated surfaces). This assessment is consistent with the current positions of the Society for Gastroenterology Nurses and Associates (SGNA)[32], the American Society of Gastrointestinal Endoscopy (ASGE)[32], and the CDC[30], the latter of which reports that, while it may be considered, EtO sterilization of the GI endoscope does not appear necessary to prevent CRE transmissions (the CDC's findings published in MMWR notwithstanding)[25].

A number of questions that this article raises about CRE, their resistance to antibiotics, and the risk of their transmission during GI endoscopy are listed in Table 1. Several reasons why the recent emergence of CRE, both in the United States and globally, is a serious public-health concern are listed in Table 2. And, Table 3 provides a number of recommended practices - for example, to clean GI endoscopes thoroughly - intended to prevent the transmission of CRE *via* a contaminated GI endoscope. For simplicity, this article's discussion is divided into two sections: the first focuses on the epidemiology and traits of CRE and their related superbugs, and the second on several outbreaks linked to GI endoscopes contaminated not only with CRE, like Hospital X's outbreak in 2013, but also with other types of infectious agents, including viruses, prior to CRE's emergence around the turn of this century.

DISCUSSION

More than any other recent report of disease transmission during GI endoscopy, Hospital X's outbreak of NDM-1-producing *E. coli* in 2013, which resulted in the infection or colonization of 38 patients who underwent ERCP, has placed the risk of CRE transmission during GI endoscopy under a powerful microscope, if not also on a front burner. Causing a new sense of urgency, the CDC's published report of this hospital's outbreak of CRE[25], coupled with the contemporaneous findings of a hospital inspection report by the CMS associating this outbreak with three contaminated ERCP endoscopes (of the same model type)[31], have heightened understandable speculation and concern about the safety and quality of GI endoscopy. Moreover, the reporting by CMS that two of Hospital X's 10 CRE-infected patients died may have irrevocably changed the landscape of infection control and endoscope reprocessing. As a direct consequence of, first, the CDC having attributed a likely cause of Hospital X's CRE outbreak (at least in part) to the physical design of the ERCP endoscope (Figure 1A and B); and, second, the CDC's observation that Hospital X's replacement of automated high-level disinfection for reprocessing its ERCP endoscopes with EtO sterilization reportedly stopped this CRE outbreak[25], it is reasonable to presume, too, that the FDA's regulatory oversight of manufacturers of GI endoscopes and related

Table 1 Several questions that this article answers

(1) What is a "superbug"?
(2) What are carbapenem-resistant *Enterobacteriaceae*, or "CRE," and their related superbugs?
(3) What are carbapenem-producing *Enterobacteriaceae*, or "CPE"?
(4) What important mechanism can cause CRE to become resistant to carbapenem antibiotics?
(5) What is a "carbapenemase" enzyme?
(6) What is a "β-lactam antibiotic" and a "β-lactam ring"?
(7) What are ESBL-producing *Enterobacteriaceae* and how do they differ from CRE?
(8) What types of infections do CRE cause?
(9) By what three mechanisms may *Enterobacteriaceae* acquire the genetic coding necessary to produce carbapenemases and become carbapenem-resistant?
(10) Prior to the emergence of CRE, what types of infectious agents have been historically transmitted during GI endoscopy?
(11) Is GI endoscopy a risk factor for CRE transmissions?
(12) What are some of the details and possible causes of the well-publicized CRE outbreak following ERCP performed by "Hospital X" in the mid-west (United States) that has recently raised public concerns about the risk of transmission of CRE during GI endoscopy?
(13) What are some of the details of other CRE outbreaks that similarly have been linked to GI endoscopy since this superbug's emergence and have been published either in the medical literature or the FDA's MAUDE database?
(14) Is high-level disinfection (whether automated or performed manually) of GI endoscopes sufficiently robust to prevent CRE transmissions? Or, is EtO sterilization of GI endoscopes required to prevent CRE transmissions?
(15) What do professional organizations including the CDC, FDA, SGNA, and ASGE currently recommend for reprocessing GI endoscopes potentially contaminated with CRE?
(16) What are some important recommendations that healthcare professionals may follow to minimize the risk of CRE transmission during GI endoscopy?

CRE: Carbapenem-resistant *Enterobacteriaceae*; GI: Gastrointestinal; EtO: Ethylene oxide gas; ASGE: American Society of Gastrointestinal Endoscopy.

Table 2 Reasons why the recent emergence of carbapenem-resistant *Enterobacteriaceae* and their related superbugs is a serious public-health concern

(1) While HAIs caused by CRE are relatively uncommon, their incidence both in the United States and globally is increasing, posing a growing public health threat[16,19,25,32]
(2) Strains of *Enterobacteriaceae* that are responsible for HAIs are becoming CRE at an alarming rate
(3) Infections of the bacterial strains that have emerged as CRE were once treatable with carbapenems, but are no longer, even though these antibiotics have been reserved by clinicians as a "last resort" or "last line" of defense for treating patients infected with multidrug-resistant bacteria
(4) CRE's resistance to carbapenems significantly limits the number of available treatment options
(5) Those very few antibiotics that remain effective for treating CRE infections are generally undesirable because, among some other limitations, they can be nephrotoxic
(6) Some strains of CRE are pan-resistant (meaning they cannot be treated using any type of antibiotic)
(7) The mortality rate of infections caused by CRE and related superbugs is relatively high (compared to carbapenem-susceptible *Enterobacteriaceae*), causing the death of as many as 50% of patients with a bloodstream infection of CRE
(8) Not only are the number of patient deaths attributed to CRE infection (from all causes, not just bacteremia) significant, both in the United States and globally, but also the rate of death among patients with CRE infections (primarily of the bloodstream) has been reported to be as much as 2 times higher than that of patients infected with carbapenem-susceptible *Enterobacteriaceae*[35]
(9) The genetic code that confers the antibiotic resistance of CRE and their related superbugs can be shared or exchanged with other bacteria of the same, or of even of a different, species (*i.e.*, "gene swapping")
(10) CRE and related superbugs are highly transmissible in the healthcare setting (and have the potential to spread in the community too)

CRE: Carbapenem-resistant *Enterobacteriaceae*; HAIs: Healthcare-associated infections.

instrumentation, including AERs, may increase. It may be that Hospital X's CRE outbreak will also cause healthcare accrediting organizations and state health departments to more closely scrutinize the infection-control and endoscope-reprocessing practices of surveyed GI endoscopy departments.

PART 1: SUPERBUGS, CARBAPENEMS, AND ACQUIRED ANTIBIOTIC RESISTANCE

Carbapenem-resistant Enterobacteriaceae, or "CRE"

"Superbugs" and "nightmare bacteria" are two monikers often used to describe certain epidemiologically important, multidrug-resistant bacteria, including CRE and other related gram-negative bacteria, that pose at least three threats to public health[17,34]. First, these bacteria are resistant to multiple classes of antimicrobial drugs. In fact, some strains of CRE are *pan*-resistant (*i.e.*, resistant to all antibiotics). Second, these resistant bacteria can share mobile pieces of genetic material, conferring their antibiotic resistance to other once-susceptible bacteria that are physically nearby and of either the same or a different species or family of bacteria. And, third, the mortality rates of patients infected with these superbugs are relatively high (compared to their antibiotic-susceptible bacterial counterparts). For example, CRE infections of the bloodstream are reportedly associated with a mortality rate of as high as 40%-50%[16,33-35],which is significantly higher than that of patients with antibiotic-susceptible bacterial bloodstream infections.

Table 3 Recommended practices for the effective reprocessing of gastrointestinal endoscopes

1 Reprocess the GI endoscope promptly after the endoscopic procedure in accordance with its manufacturer's step-by-step set of instructions
(1) As required, supplement these instructions with the recommendations of published infection-control guidelines
(2) Always reprocess the GI endoscope's air/water channels (Also, always reprocess the GI endoscope's suction and air/water valves and other accessories)
(3) Before its reprocessing, visually examine the GI endoscope, especially its distal sheath, for excessive wear and tear, having it servicing when required
(4) Practice Standard Precautions when reprocessing GI endoscopes (As required, also employ Contact Precautions to prevent CRE transmission)
(5) Confirm that the high-level disinfectant is contacting all of the GI endoscope's potentially contaminated surfaces
(6) The use of ethylene oxide (EtO) gas to sterilize ERCP endoscopes, in lieu of high-level disinfection, may be considered. (No matter, thorough cleaning of the endoscope is required)
2 Place emphasis on cleaning and brushing (prior to high-level disinfection) the area near, around and behind the ERCP endoscope's forceps elevator (Figure 1B)
(1) Ensure that, if it is exposed, the ERCP endoscope's elevator wire channel, which houses the cable that controls and angulates this forceps elevator, is thoroughly flushed with a detergent solution. The complete manual reprocessing (*i.e.*, cleaning, high-level disinfection, and drying) of this (exposed) channel may be necessary for some ERCP endoscope models, to prevent disease transmission
(2) Routinely train and evaluate the knowledge of reprocessing staffers
(3) Periodically audit reprocessing staffers' practices to verify the proper cleaning and brushing of all models of GI endoscopes, especially the ERCP endoscopes[61]
(4) Use cleaning brushes and detergents that have been validated, recommended, and/or "approved" for use by the GI endoscope's manufacturer[31,62,63]
(5) Manually "leak test" the GI endoscope prior to its cleaning in accordance with its manufacturer's instructions (unless otherwise instructed by the automated endoscope reprocessor's [or, AER's] manufacturer, if the AER is equipped with an automated leak tester)
3 Routinely monitor (*i.e.*, at least once a day, if not more often) the concentration of the high-level disinfectant to ensure its effectiveness. Record the results in a log book or use an electronic format that permits archiving and documentation retreival
(1) In addition to its concentration, verify and record for each processed GI endoscope that the high-level disinfectant's immersion time and temperature are appropriate
4 Use bacteria-free (or sterile) water to rinse the GI endoscope following its high-level disinfection
(1) Compliance with this instruction may require: (A) proper maintenance and replacement of a water filtration system, if one is used; and (B) routine monitoring of the rinse water to confirm its lack of bacteria[64]
5 Consider using sterile water in the water bottle for lens cleaning and irrigation during GI endoscopy, especially during ERCP[15,65]
6 Terminally dry all of the GI endoscope's internal channels (including the ERCP elevator wire channel, if it is exposed) using 70% alcohol and forced air[5,66]
7 Store the GI endoscope with its insertion tube hanging freely and vertically in a clean, dry, and well-ventilated area or cabinet[66,67]
(1) Consider reprocessing the GI endoscope again before its reuse if it has been stored for more than 5 d[68]. Reprocessing ERCP endoscopes before each use may be advisable
8 If using an AER, ensure that it is performing properly; has been validated for the effective reprocessing of each GI endoscope in inventory; has been serviced and maintained as required; and that its internal surfaces and components are being routinely self-disinfected as instructed by its manufacturer
9 Manufacturers may consider enhanced design controls and validation measures to ensure the adequate reprocessing of ERCP endoscopes and other complex reusable instrumentation, to further minimize the risk of disease transmission during GI endoscopy

CRE: Carbapenem-resistant *Enterobacteriaceae*; GI: Gastrointestinal.

According to the CDC, more than 2 million people are infected with a superbug each year in the United States, and at least 23000 die as a consequence, with the overuse of antibiotics being cited by the CDC as the primary cause of the emergence of CRE and other superbugs[34]. [Note: Although not a focus of this article, other well-known organisms also commonly referred to as "superbugs" include vancomycin-resistant enterococci (VRE) and methicillin-resistant staphylococcus aureus (MRSA), both of which are gram-positive bacteria]. As their name betrays, CRE are resistant to carbapenems, which are a class of antimicrobial drugs known as broad-spectrum β-lactam antibiotics. This is a concerning trait, because these "big gun" antibiotics have been used by clinicians as a "last line" of defense, or "last resort," for treating many types of serious infections caused by multidrug-resistant gram-negative bacteria[17,34]. CRE's resistance to carbapenem antibiotics - specific examples of carbapenems include doripenem, ertapenem and imipenem - significantly limits the number of available treatment options. And the very few antibiotics that remain effective for treating CRE-infected patients are generally undesirable because of their adverse side-effects, which can include nephrotoxic reactions. These and other reasons discussing why the recent emergence of CRE and their related superbugs is a growing public health concern are summarized in Table 2.

CRE are members of the large *Enterobacteriaceae* family, which both includes more than 70 genera and is the largest collection of medically important gram-negative bacilli. Many of the species of bacteria in this family (whether or not multidrug-resistant) are "enteric" (*i.e.*, they commonly reside in the normal, healthy intestinal flora of humans and other types of animals) and "opportunistic" (*i.e.*, they ordinarily cause disease only in patients with weakened or compromised immune systems). Examples of some of this family's genera include: *Klebsiella*, *Salmonella*, *Enterobacter*, and *Serratia*. Being non-spore forming (vegetative) bacteria, *Enterobacteriaceae* are readily destroyed by not only high-level disinfection (and sterilization and other harsh environmental conditions), but also by intermediate-level disinfection, and usually even by low-level disinfection.

The increasing resistance of once-susceptible strains of *Enterobacteriaceae* to carbapenems is relatively recent, with the first documented case of CRE infection occurring in a patient in North Carolina (United States), in 2001[17]. Emergent species of CRE include: *K. pneumoniae*,

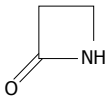

Figure 2 Displayed is the β-lactam ring's four-membered (*i.e.*, a square) chemical structure.

which is the most commonly encountered species of CRE in the United States; *E. coli*; and *Enterobacter cloacae*. Because CRE can be spread through direct or indirect contact with feces (and other infectious materials), not only (among other practices) is proper hand hygiene necessary to interrupt their transmission in the healthcare setting, but also, as this article found, GI endoscopy is a confirmed risk factor for infections and colonizations of CRE and their related superbugs[25,31]. While still relatively low, the incidence of healthcare-associated infections (HAIs) caused by CRE and their related superbugs in acute-care hospitals, both in the United States and globally, has increased significantly during the past decade, posing a growing and serious public health threat (Table 2)[16,19,25,32]. According to the CDC, data from one national surveillance system suggest that the proportion of *Enterobacteriaceae* in the United States that have acquired a resistance to carbapenems (*i.e.*, CRE) has increased more than 3-fold, from 1.2% in 2001 to 4.2% in 2011[16].

Without effective antimicrobial drugs to treat them, infections of CRE following a medical procedure could prove to be even more insidious to public health than those caused by HIV 30 years ago, and since. Indeed, in contrast to infections caused by CRE, HIV infection: (1) can be controlled with (anti-viral) drugs (whereas some CRE strains are pan-resistant); (2) is not associated with a mortality rate of as high as 50% (like that of CRE infections of the bloodstream); and (3) requires only Standard Precautions to prevent its spread (whereas Contact Precautions may be additionally required to prevent the spread of CRE in the healthcare setting). Further, HIV is not ordinarily transmitted from one patient to another due to poor hand hygiene, but rather is generally spread only through exposure to infected blood or other infectious fluids and materials (whereas CRE infections can be a consequence of poor hand hygiene). And, although outbreaks of CRE linked to contaminated GI endoscopes, with associated morbidity and mortality, have been reported and no longer are rare adverse events[13,20-22,33,36-39], HIV transmission during GI endoscopy has not been documented.

Carbapenemases, *β-lactam antibiotics*, *and the β-lactam ring*

As discussed, carbapenems are not an effective treatment for patients infected with CRE. An understanding of one important mechanism that renders CRE and their related superbugs resistant to carbapenems requires some knowledge about the molecular structure of these antimicrobial drugs. Carbapenems are a type of β-lactam antibiotic, and - like that of all β-lactam antibiotics, including cephalosporins, monobactams, and penicillins, the latter of

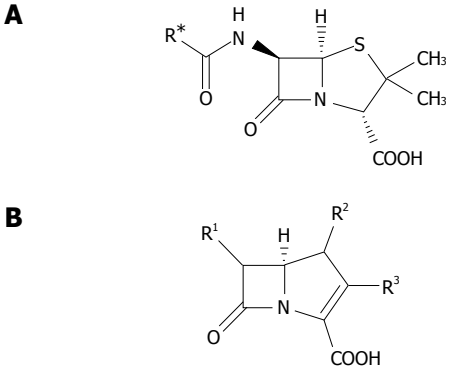

Figure 3 Displayed are the core chemical structures of two different types of β-lactam antibiotics: A penicillin and a carbapenem. Both antibiotics feature the four-membered β-lactam ring. A: The core chemical structure of penicillin antibiotics; B: The core chemical structure of carbapenem antibiotics. (*The "R" in either diagram denotes a distinct side chain that is attached to the molecule's core).

which are the archetype of β-lactam antibiotics - the core molecular structure of carbapenems features a β-lactam ring. The four-membered chemical structure of this ring is displayed in Figure 2. The respective molecular structure of a penicillin and of a carbapenem, each necessarily featuring the characteristic β-lactam ring (Figure 2), is displayed in Figure 3A and B, respectively.

The resistance of *Enterobacteriaceae* to carbapenem antibiotics may be mediated by a number of different mechanisms, although only one is the focus of this review: through their synthesis (or production) of carbapenemases, which are a type of enzyme, known as a β-lactamase enzyme, that hydrolyzes (*i.e.*, chemically breaks down) the β-lactam ring (Figure 2) of carbapenems (and other β-lactam antibiotics) (Figure 3). (Other mechanisms that confer a bacterium's resistance to an antibiotic include the active removal of the antibiotic from inside the bacterium's cell, or through the chemical modification of the bacterium's target site so that the antibiotic no longer recognizes it). Through this one particular mechanism, *Enterobacteriaceae* that are inherently with, or that have acquired, the genetic material (*i.e.*, DNA) necessary to produce carbapenemases can (but do not always) display a resistance to carbapenems, generally precluding the use of these antibiotics to treat infected patients. These resistant bacteria are a specific type of CRE known as carbapenemase-producing *Enterobacteriaceae*, or "CPE", which are responsible for most CRE-related outbreaks encountered in the clinical setting, including Hospital X's aforementioned CRE outbreak[25]. (While CPE are a type of CRE, not all CRE are CPE; mechanisms other than the resistant bacteria's production of carbapenemases can cause CRE to be resistant to carbapenems).

Extended-spectrum β-lactamase enzymes

Until recently, bacteria in the *Enterobacteriaceae* family rarely carried the genetic material necessary to synthesize carbapenemase enzymes. As a result, carbapenems were usually an effective treatment for patients infected with these (carbapenem-susceptible) bacteria, including challenging

Enterobacteriaceae that produce another type of enzyme called extended-spectrum β-lactamases, or "ESBLs". Indeed, carbapenem antibiotics remain indicated for the treatment of serious infections caused by ESBL-producing *Enterobacteriaceae* (but not those caused by CRE). Reportedly in response to the overuse of antibiotics[34], however, while some strains of *Enterobacteriaceae* remain susceptible to carbapenems, others have acquired the genetic material necessary to produce carbapenemases through the process of natural selection, heralding CPE's recent emergence. [Note: In this context "natural selection" is defined as a process by which surviving and multiplying bacteria have adapted to their environment. In contrast, those bacteria that do not adapt to their changing environmental conditions generally become extinct. Further, antibiotics can present a "selective pressure" that destroys susceptible, unadapting bacteria, but that, for those bacteria that undergo natural selection and become resistant to the antibiotics, have little or no effect].

Carbapenems were ironically developed a generation ago to treat patients infected with those strains of *Enterobacteriaceae* that had begun to display a resistance to cephalosporins, which previously had been an effective antibiotic treatment for patients infected with these bacteria. This displayed resistance to cephalosporins was predominantly due to these bacteria's production of ESBLs. Like carbapenemases, ESBLs chemically hydrolyze (*i.e.*, break down and inactivate) the β-lactam ring of cephalosporins, rendering these β-lactam antibiotics ineffective. ESBL enzymes are distinct from carbapenemase enzymes, however, and while ESBL-producing *Enterobacteriaceae*, which are a type of superbug similar to but not CPE, are resistant not only to cephalosporins but also to most other types of β-lactam antibiotics, including penicillins, they (unlike CRE) currently remain susceptible to carbapenems.

Carbapenemase-producing Enterobacteriaceae, or CPE

CPE produce several different types of carbapenemase enzymes, three of which this article discusses.

KPC-producing *Enterobacteriaceae*: The most commonly identified carbapenemase in the United States produced by certain CRE (namely, CPE) is *K. pneumoniae* carbapenemase, or "KPC". Isolated for the first time in North Carolina (United States), in 2001, from a patient infected with a carbapenem-resistant strain of *K. pneumoniae*, KPC has since spread around the world. Logically, strains of *K. pneumoniae* that produce KPC are called KPC-producing *K. pneumoniae*, and, although it reportedly did not infect or colonize any of Hospital X's 38 affected patients, the CDC recovered this specific type of CRE from the implicated ERCP endoscope during its investigation of Hospital X's CRE outbreak in 2013[25]. Encoded by a highly transmissible gene known as the "*bla*$_{KPC}$" gene, the KPC enzyme is no longer exclusively produced by *K. pneumoniae*, however. [Note: "*bla*" refers to the gene that is responsible for the bacterium's production of the said β-lactamase enzyme and, therefore, for the bacterium's antibiotic resistance. For example, "*bla*$_{KPC}$" refers to the gene (often, but not always, of *K. pneumoniae*) that is responsible for the production of the subscript-noted enzyme - in this example, of the KPC enzyme]. Due to the concerning ability of CRE (and other superbugs) to share genetic material that confers antibiotic resistance, KPC (although first identified in and still predominantly produced by *K. pneumoniae*) has also been recently identified in other genera and families of gram-negative bacteria that have acquired the *bla*$_{KPC}$ gene - for example, in *E. coil*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. (*i.e.*, KPC-producing *E. coli*, KPC-producing *P. aeruginosa*, *and* KPC-producing *Acinetobacter* spp., respectively, the latter two of which are not *Enterobacteriaceae*). [Note: *P. aeruginosa*, like *Klebsiella* spp. and *E. coli*, is a gram-negative (non-spore-forming vegetative) bacterium. But, unlike these other two, which are members of the *Enterobacteriacae* family, *P. aeruginosa* is of the *Pseudomonadaceae* family and therefore, while some of its strains may be classified as *bona fide* "superbugs," it is not CRE. Similarly, *Acinetobacter* spp. are of the *Moraxellaceae* family, and those bacteria within this family that have acquired the *bla*$_{KPC}$ gene and are resistant to carbapenems are not CRE, although, too, may be classified as superbugs].

NDM-producing *Enterobacteriaceae*: Described first in 2009 in a European patient infected with an antibiotic-resistant bacterium while traveling to India, the NDM-1 (New Delhi metallo-β-lactamase-1) enzyme is a second example of a carbapenemase[18]. [Note: The number "1" associated with the initials "NDM" denotes specificity to the NDM enzyme. NDM-2 and NDM-3, for example, are variants of NDM-1 and therefore are similar, but different, enzymes, featuring unique amino acid substitutions compared to the NDM-1 enzyme and to one another]. This infected patient was unsuccessfully treated while in a New Delhi hospital, and, after the patient's repatriation to Europe, a carbapenem-resistant strain of *K. pneumoniae* bearing (not the *bla*$_{KPC}$ gene, but the) the *bla*$_{NDM-1}$ gene was identified as the infection's cause. (In this section's example, *bla*$_{NDM-1}$ refers to the gene of the *K. pneumoniae* bacterium that is responsible for its production of the NDM-1 enzyme). NDM-1 is referred to as a metallo-β-lactamase (MBL) enzyme because it uses a metal ion (*i.e.*, zinc) to catalyze the hydrolysis of (that is, to chemically inactivate) carbapenems and other β-lactam antibiotics. In addition to identifying the newly described resistance mechanism of NDM-1 for the first time in the United States, a report in 2010 described, also for the first time in the United States, MLB-producing *Enterobacteriaceae*[19]. And, NDM-1 was isolated for the first time from a (carbapenem-resistant) strain of *P. aeruginosa* (which is of the *Pseudomonadaceae* family and therefore, while a superbug, it is not CRE) in *Serbia*[40], in 2011, and in the United States (Delaware)[41], in 2014.

The most common CRE that produce the NDM-1 enzyme include NDM-1-producing *K. pneumoniae*, the resistance of which is conferred by the *bla*$_{NDM-1}$ gene; and NDM-1-producing *Enterobacter cloacae* (the resistance of which is also conferred by the *bla*$_{NDM-1}$ gene). As previously discussed, NDM-1-producing *E. coli* was the specific bacterial strain that the CDC determined in 2013 was responsible for the outbreak of CRE at Hospital X

following ERCP[25,28]. While not of the *Enterobacteriaceae* family and therefore not CRE, carbapenem-resistant strains of *Acinetobacter* spp. (*i.e.*, *Acinetobacter baumannii*), in addition to producing KPC (*via* the acquired *bla*KPC gene), have also been found in the clinical setting to produce NDM-1 (*via* the acquired *bla*NDM-1 gene) and NDM-2 (*via* the acquired *bla*NDM-2 gene).

VIM-producing *Enterobacteriaceae*: First identified in Italy, Verona integron-encoded metallo-β-lactamase, or "VIM," is a third example of a carbapenemase enzyme produced by certain carbapenem-resistant bacteria (*i.e.*, CPE). This enzyme was initially isolated from *P. aeruginosa* (which, again, is not a CRE), with a variant of this enzyme (*i.e.*, VIM-1) being isolated from *Enterobacteriaceae,* namely from VIM-producing *K. pneumoniae* (or VPKP), in the United States in 2010[42]. Similar to the KPC enzyme's production being encoding by the transmissible "*bla*KPC" gene, production of the VIM enzyme is encoded by the *bla*VIM gene. The production of KPC and VIM by strains of CRE confers their resistance (through hydrolysis) to carbapenems.

CRE's acquired resistance to carbapenem antibiotics

In general, bacteria may acquire the genes necessary to become resistant to an antibiotic drug by one of a number of different mechanisms - for instance, through a naturally inherited genetic trait. Virtually all bacteria in the *Enterobacteriaceae* family naturally produce certain β-lactamase enzymes that confer their intrinsic resistance to penicillins (but not carbapenems). Another example is through a spontaneous mutation of their existing genetic material, with the newly acquired resistance-conferring trait being passed on to subsequent generations (*e.g.*, natural selection). (The overuse of antibiotics is a type of "selective pressure" that reportedly has caused bacteria, through natural selection, to acquire the necessary genetic material to synthesize enzymes, such as carbapenemases and ESBLs, that inactivate and render ineffective one or more types of antibiotics, such as carbapenems and cephalosporins, respectively). And a third mechanism by which bacteria may acquire the genes necessary to become resistant to an antibiotic drug is through the acquisition of new genetic material from other, already-resistant bacteria of either the same or of a different bacterial species (or family), with this newly acquired resistance-conferring genetic material being passed on to subsequent generations. An example of this type of "gene sharing" is the horizontal transfer of the blaKPC gene from carbapenemase-producing *K. pneumoniae* to carbapenem-susceptible *E. coli*, resulting in the latter becoming KPC-producing *E. coli.*

Risk factors for CRE infection

Independent factors that increase a patient's risk of becoming infected with CRE include: (1) prior treatment with carbapenems or another antibiotic (*e.g.*, fluoroquinolones and broad-spectrum cephalosporins); (2) receiving treatment in an intensive care unit (ICU); (3) having received mechanical ventilation; (4) being elderly; (5) being immuno-suppressed (*e.g.*, patients receiving an organ or stem cell transplant); (6) the placement of a central venous catheter; and (7) having diabetes. Undergoing GI endoscopy, especially ERCP, now also has been identified as a risk factor for CRE infection[25-31,33]. To be sure, Hospital X's outbreak in 2013 is the most publicized instance in the United States directly linking GI endoscopes contaminated with CRE to patient morbidity and/or mortality[31]. To date, only patients receiving medical treatment in hospitals (*i.e.*, HAIs), long-term acute care facilities, and nursing homes are reportedly prone to CRE infection. According to the CDC, however, *Enterobacteriaceae* that are resistant to carbapenems (*i.e.*, CRE) will soon also be responsible for infections in community settings[34].

Types of CRE infections, treatment options

In addition to biliary tract infections and other type of infections associated with contaminated GI endoscopes[25], CRE can cause urinary tract infections (or UTIs, which are the most common types of CRE infections); wound infections; bloodstream infections (which, as previously noted, are associated with a 40%-50% mortality rate); and ventilator-associated pneumonia. While very few antibiotics are effective for treating patients infected with CRE, drug treatment may include the administration of polymyxins. These are an older type of antibiotic drug that includes colistin, and, while effective against most gram-negative bacilli and some strains of CRE, polymyxins can have toxic side-effects. Tigecycline may also be used to treat certain CRE infections, but this antibiotic drug achieves poor serum levels, limiting its clinical effectiveness and, therefore, its use.

PART 2: GI ENDOSCOPY

Although the risk of disease transmission during GI endoscopy is reported to be low, infections and outbreaks due to contaminated GI endoscopes, with associated patient morbidity and mortality, have been documented a number of times during the past 30 years, both prior to and since CRE's emergence[2,4-12,14,33,34]. These cases include infections of bacteria, including *P. aeruginosa*, and viruses, namely, the hepatitis B (HBV) or C virus (HCV). Like their emergence in the United States and globally, only during the past few years has the transmission of CRE been linked to GI endoscopy[13,20-22,25,33,36-39]. While for historical purposes, contextual insight, and important perspective a number of cases of disease transmission during GI endoscopy prior to CRE's emergence are discussed below, this section's primary focus in placed on outbreaks of CRE and their related superbugs due to a contaminated GI endoscope.

Types of infectious agents transmitted during GI endoscopy prior to CRE's emergence

Prior to the turn of this century and CRE's emergence, infections and outbreaks due to contaminated GI endoscopes (while infrequent) had been reported, most often being attributed to the transmission of *P. aeruginosa* during ERCP, and less commonly to the transmission of other types of bacteria including *Enterobacteriaceae* (*e.g.*, *Salmonella* spp., *Klebsiella* spp. and *Serratia* spp.) during either esophagogastroduodenoscopy (or, "EGD")

or colonoscopy[33]. (Prior to 2001 the resistance of these transmitted strains of *Enterobacteriaceae* to carbapenems in the United States and globally was rare). The specific breach typically responsible for these instances of disease transmission was reported to be, as much if not more so than faulty cleaning and inadequate high-level disinfection, insufficient drying of one or more of the GI endoscope's several internal channels, particularly the exposed elevator wire channel of some models of ERCP endoscopes, using either manual reprocessing procedures or an AER[7-9,11,12,14]. In only a very few cases has the transmission of a bloodborne virus (*i.e.*, HBV or HCV) been reported during GI endoscopy, with the un-sterile administration of an *iv* medication typically being identified as, or suspected of being, the outbreak's proximate cause or a likely contributing factor[9,10]. And, no cases of the transmission of HIV due to a contaminated GI endoscope have been reported, either prior to or since CRE's emergence. Providing some crucial insight and conclusions about the corrective actions necessary to prevent the transmission of superbugs during GI endoscopy in later years, the circumstances of several outbreaks reported prior to CRE's emergence are discussed below. Whether the actual risk of infection *via* a contaminated GI endoscope is significantly higher than reported (*e.g.*, 1 in 1.8 million), due to under-reporting, the lacking surveillance of post-endoscopic infections, and "missed" infections, has been suggested[33,43].

Specific instances of disease transmission during GI endoscopy prior to CRE's emergence

With historical and clinical significance, several reported instances of disease transmissions during GI endoscopy occurred prior to the emergence of CRE. For example, Birnie *et al*[9] (1983) report a case of patient-to-patient transmission of HBV during GI endoscopy. These authors conclude that the failure to clean, high-level disinfect, and dry the air/water channels of a gastroscope was likely the cause of HBV transmission. While recommending that these channels be thoroughly high-level disinfected to prevent infection, Birnie *et al*[9] (1983) also suggest consideration of EtO gas (in lieu of high-level disinfection) to sterilize GI endoscopes potentially contaminated with HBV. (The replacement of high-level disinfection with EtO sterilization was the same measure that Hospital X implemented in 2013 to stop its CRE outbreak[25-31]). Similarly, Bronowicki *et al*[10] (1997) report transmission of the HCV from one patient to two others during colonoscopy. These authors conclude that inadequate cleaning of the colonoscope's working (or instrument) channel; inadequate disinfection of the colonoscope (a 5-min immersion in 2% glutaraldehyde instead of a 20-min immersion as guidelines recommend); and the failure to sterilize the reusable biopsy forceps were likely responsible for this outbreak. This report notes, however, the possibility that the improper, un-sterile administration of *iv* medications was the cause of HBV transmission.

Cryan *et al*[11] (1984) report an outbreak of *P. aeruginosa* following ERCP, with associated patient morbidity and mortality. This report concludes that this outbreak was related to inadequate high-level disinfection of the ERCP endoscope's air/water channels. Following the introduction of a modified reprocessing technique, which involved rinsing the ERCP endoscope's air/water channels with a disinfectant, no further *P. aeruginosa* infections were identified. Allen *et al*[7] (1987) also report an outbreak of *P. aeruginosa* following ERCP. These authors conclude that this outbreak was due, in part, to the failure by an AER to dry every one of an ERCP endoscope's internal channels, including its exposed elevator wire channel. According to this report, another contributing factor to disease transmission was likely the contamination of the internal structures and components of the AER used to reprocess the ERCP endoscopes. The outbreak ended only once 70% alcohol was manually suctioned through the ERCP endoscope's channels followed by their being dried.

Similarly, Alvarado *et al*[8] (1991) document an outbreak of *P. aeruginosa* following upper GI endoscopy, including ERCP, due to the faulty design of an AER, which resulted in the contamination of the water used by the AER to rinse the GI endoscopes after high-level disinfection. According to these authors, this outbreak, like the outbreak reported by Allen *et al*[7] (1987), was terminated only once the GI endoscopes, disinfected using the faulty AER, were terminally rinsed with 70% alcohol followed by forced air drying[8]. And, Streulens *et al*[12] (1993) report an outbreak of *P. aeruginosa* and of three strains of *Enterobacteriaceae* (namely, *K. pneumoniae*, *Enterobacter cloacae*, and *S. marcescens*) following ERCP. These different bacteria were isolated from the GI endoscope and/or the AER used for reprocessing. Improper reprocessing and drying of the ERCP endoscopes were reportedly at fault. These authors report that the outbreak was terminated once: the ERCP endoscope's (exposed) elevator-wire channel was properly high-level disinfected; all of the ERCP endoscope's channels were flushed with 70% alcohol and air dried; and the AER's internal components were themselves disinfected[12].

In summary, infections and outbreaks due to contaminated GI endoscopes prior to CRE's emergence were typically caused by *P. aeruginosa* (likely of an exogenous origin) infecting patients during ERCP. Less frequently reported were patient-to-patient transmissions of HBV and HCV. Whereas improper reprocessing, in general, and inadequate drying of the ERCP endoscope's exposed elevator wire channel, in particular (whether performed manually or using an AER), were often reported to be responsible for bacterial infections following GI endoscopy, viral transmissions, in contrast, were (and are today) often reported to be due to either the improper cleaning of the GI endoscope (or endoscopic accessory) or, possibly more often, to the un-sterile administration of an *iv* medication during GI endoscopy.

Transmission of CRE and related superbugs during GI endoscopy

Like the aforementioned report published in MMWR discussing the CDC's investigation of Hospital X's CRE

outbreak in 2013[25-31], a number of other reports published in the medical literature since CRE's emergence similarly document infections and colonizations of CRE and their related superbugs due to a contaminated GI endoscope, most often (as prior to CRE's emergence, too) to an ERCP endoscope[13,20-22,24,33,36-39]. [Note: The ERCP endoscope's unique and complex physical design - coupled with the increased invasiveness of, and complication rate associated with, ERCP especially in the presence of biliary tract obstruction and tissue injury - may explain why bacterial infections including those caused by CRE are more often associated with ERCP than with any other type of GI endoscopic procedure (Figure 1)[7,11,20-22,25]]. Providing crucial insight into both the causes and prevention of CRE transmissions during GI endoscopy, several of these recently published reports conclude that the ERCP endoscope's physical design likely contributed to the transmission of CRE or a related superbug[13,20-22,24-30].

For example, Carbonne *et al*[22] (2010) discuss a multi-hospital outbreak of CRE identified in a suburb south of Paris, France, in 2009, with 8 documented cases of infection or colonization due to KPC-producing *K. pneumoniae* following ERCP. According to this report, this outbreak highlights the risk of transmissions of CRE and related multidrug-resistant bacteria during GI endoscopy, particularly during ERCP. Carbonne *et al*[22] (2010) conclude that a single ERCP endoscope was a "persistent source" of contamination and the mode of transmission of the outbreak's CRE strain. Publishing findings similar to these authors, Alrabaa *et al*[20] (2013) reported that, between June, 2008, and January, 2009, 7 patients in Florida (United States) were infected or colonized with KPC-producing *K. pneumoniae* following ERCP performed at one endoscopy center (shared by two hospitals). Infection sites included blood, bile, and urine, and one of the infected patients died during hospitalization. Whether this report documents the first instance of CRE transmission in the United States *via* a contaminated GI endoscope is unclear.

Consistent with both the CDC's report discussing Hospital X's CRE outbreak[25] and Carbonne *et al*[22]'s (2010) report, both of which implicate the ERCP endoscope's complex physical design as likely responsible for disease transmission, Alrabaa *et al*[20] (2013) found the suspect GI endoscope's "elevator area" to be contaminated with carbapenemase-producing *E. coli* (not the outbreak's strain of KPC-producing *K. pneumoniae*), due to "inadequate cleaning of the complex terminal part of the ERCP scope." Acknowledging that the ERCP endoscope is particularly difficult to clean because its distal tip features a "small tube with a complex design including a small mobile metal piece called the 'elevator'," Alrabaa *et al*[20] (2013) conclude that the contaminated GI endoscope itself was the source of this outbreak's CRE strain. According to this report, the ERCP endoscope's "elevator piece" was not cleaned in accordance with the manufacturers' instructions and "needs additional manual cleaning using a brush prior to standard scope processing," to prevent disease transmission and ensure that this elevator piece does not harbor "dangerous microorganisms" or "biodebris" that Alrabaa *et al*[20] (2013) found remained under the elevator piece of the implicated scope after it was presumably cleaned.

Discussing another outbreak in Clermont-Ferrand, France, Aumeran *et al*[21] (2010) report that 16 patients were infected or colonized with an ESBL-producing *K. pneumoniae* following ERCP performed between December, 2008 and August, 2009. (As previously discussed, whereas CRE are resistant to both types of antibiotics, ESBL-producing *Enterobacteriaceaea*, a related superbug, are resistant to cephalosporins, but not carbapenems). Like the conclusions of the CDC's report in MMWR and of the findings of both Carbonne *et al*[21] (2010) and Alrabaa *et al*[20] (2013), Aumeran *et al*[21] (2010) further report that the outbreak's strain "was finally isolated from one duodenoscope (*i.e.*, an ERCP endoscope)." Specifically, these authors report that: (1) ERCP endoscopes "can act as a reservoir" for ESBL-producing *K. pneumoniae* and other types of multi-drug resistant bacteria; (2) contamination of the ERCP endoscopes persisted "despite repeated disinfections"; (3) these ERCP endoscopes are "difficult to clean and disinfect" and are of a design that precludes detachment of their distal tip, making "mechanical removal of the distal debris in the elevator wire channel more difficult"; and (4) "appropriate mechanical flushing and cleaning with detergent of the raiser channel that contains the elevator wire is an essential step for these devices"[21].

Similarly, Bajolet *et al*[13] (2013) reported an outbreak at a hospital in Reimes, France, in 2011, linked to a single gastroscope contaminated with ESBL-producing *P. aeruginosa*, which is yet a third type of gram-negative, multidrug-resistant superbug related to (but not) CRE. In addition to having identified some important breaches in the manual cleaning of the gastroscope, Bajolet *et al*[13] (2013) report that a minor defect, namely, wear of adhesive at the gastroscope's distal sheath, "may have contributed to the development and persistence of bacterial biofilm in this case". This report highlights the importance of, not only the potential contribution of the GI endoscope's physical design to HAIs, but also the proper servicing, maintenance, and visual inspections of GI endoscopes to the prevention of patient-to-patient transmission of CRE. And, Naas *et al*[24] (2010) reported an outbreak in France caused by a single contaminated side-viewing duodenoscope's transmission of KPC-producing *K. pneumoniae*. To prevent infection, these authors recommend: (1) prompt reprocessing of the GI endoscope after its use - not as many as 24 h later during which time patient debris may dry and harden on the endoscope, becoming more difficult or remove during cleaning; (2) assuring thorough drying of the GI endoscope's internal channels; and (3) microbiologically sampling the GI endoscope several times a year, to evaluate its channels and other surfaces for bacterial contamination.

Like those published in the peer-reviewed medical literature, a number of reports recently filed in the FDA's MAUDE database by hospitals and manufacturers of GI endoscopes and related medical equipment (but without identifying the medical facility by its name), as a regulatory

Table 4 Several reports of outbreaks of carbapenem-resistant *Enterobacteriaceae* (or a related superbug) following gastrointestinal endoscopy that were filed in the Food and Drug Administration's MAUDE database between 2012 and 2014 by manufacturers of gastrointestinal endoscopes and related medical equipment

Reports filed in 2014:
(1) Food and Drug Administration. Report date: May 2, 2014. Report number: 2951238-2014-00225. (Infections or colonizations of patients following ERCP with an extended β-lactamase [ESBL] strain of *E. coli* strain. Also refer to Report number: 2951238-2014-00004)
(2) Food and Drug Administration. Report date: March 7, 2014. Report number: 2518897-2014-00001[36]. (Infections or colonizations of patients following ERCP with CRE)
(3) Food and Drug Administration. Report date: January, 28, 2014. Report number: 2951238-2014-00027[38]. (Infections or colonizations of patients following ERCP with CRE)
(4) Food and Drug Administration. Report date: January 16, 2014. Report number: MW5033987[39]. (Infections or colonizations of patients following ERCP with CRE)
(5) Food and Drug Administration. Report date: May 27, 2014. Report number: MW5036408. (One patient infected or colonized with CRE following ERCP)
Reports filed in 2013:
(1) Food and Drug Administration. Report date: March 4, 2013. Report number: MW5029305[37]. (Infections or colonizations of patients following ERCP with CRE)
(2) Food and Drug Administration. Report date: September 30, 2013, and October 28, 2013. Report number: 2518897-2013-00005. (Also refer to Report number: 2523209-2013-00013). Note: This report was presumably filed by Hospital X documenting its CRE outbreak identified between January and September, 2013
Reports filed in 2012:
(1) Food and Drug Administration. Report date: September 25, 2012. Report number: 8010047-2012-00404. (Infections or colonizations of patients following ERCP with a multidrug-resistant *E. coli*)
(2) Food and Drug Administration. Report date: November 21, 2012. Report number: 8010047-2012-00454. (Possible infections or colonizations of patients following ERCP with *E. coli*; the bacterial strain is not necessarily resistant to antibiotics; and this incident may be a pseudo-outbreak, not true infections or colonizations)

These reports, which do not identify the medical facility by name, associate a contaminated ERCP endoscope with a confirmed patient infection or colonization, or with an outbreak of CRE or a related superbug. (Some of these reports are included in this article's reference section. This table's listed reports for each year may not be inclusive of every report filed in that year). CRE: Carbapenem-resistant *Enterobacteriaceae;* GI: Gastrointestinal.

requirement, provide crucial information into the causes of, risk factors for, and prevention of CRE transmissions during GI endoscopy[36-39] [Note: The MAUDE database features medical device reports mandatorily submitted to the FDA by certain entities (*e.g.*, manufacturers) and voluntarily reported by health care professionals, patients and consumers]. These reports almost exclusively cite a contaminated ERCP endoscope as the likely cause of a confirmed infection or outbreak of CRE or their related superbugs following GI endoscopy. Several of these reports filed in 2012, 2013 and 2014 are listed in Table 4, including the report in the MAUDE database documenting Hospital X's outbreak. (Outbreaks of CRE linked to contaminated GI endoscopes in the United States and identified in the MAUDE database were most common in 2014, one reason for which may be that CRE and its related superbugs have only recently emerged). But, as with infections of carbapenem-susceptible bacteria linked to GI endoscopy, whether the actual incidence of CRE transmissions due to a contaminated GI endoscope is significantly higher than reported in the medical literature and the FDA's MAUDE database, due to, for example, under-reporting, is unclear, although possible[43].

In summary, several reports of infections and colonizations in the United States and Europe (often France, the reasons for which are unclear) due to a GI endoscope, most often to an ERCP endoscope, contaminated with CRE or a related superbug have been published during the past few years, both in the peer-reviewed medical literature and the FDA's MAUDE database (Table 4). These reports frequently cite the physical design of the GI endoscope as a factor contributing to disease transmission, often adding that the ERCP endoscope's "forceps elevator" or "elevator area" is difficult to clean and typically the surface of the endoscope contaminated with the outbreak's superbug strain (Figure 1B), despite these investigations typically reporting that this surface was reprocessed[20-22,25]. In one instance (*i.e.*, Hospital X's CRE outbreak), the replacement of automated high-level disinfection of the GI endoscope with EtO sterilization terminated the CRE outbreak[25,31]. For each of these reports, whether the outbreak's strain of CRE or their related superbugs originated in the environment (*e.g.*, contaminated water) or was patient-borne is typically not determined or clarified[21].

Transmission of CRE and related superbugs during other types of flexible endoscopic procedures

A demonstrated public health threat both in the United States and globally, transmissions of CRE are not exclusive to GI endoscopy. Other types of flexible endoscopic procedures, including bronchoscopy and cystoscopy (as well as other types of medical procedures unrelated to flexible endoscopy), are also identified risk factors for infections (and predictors for colonizations) with CRE and related superbugs[23,44,45]. Indeed, some infection-control measures designed to prevent CRE transmission during GI endoscopy may also be employed during these other flexible endoscopic procedures for the successful prevention of infection. For example, Koo *et al*[23] (2012) discuss an outbreak of NDM-1 *K. pneumoniae* linked to contamination of the video camera head of urological instrumentation. Chang *et al*[44] (2013) similarly report a CRE outbreak at a regional teaching hospital in southern Taiwan, finding an ureteroscope contaminated with ertapen-

em-resistant *E. cloacae* (a type of CRE) to be responsible for several UTIs. Chang *et al*[44]'s (2013) findings are not entirely surprising, since UTIs are the most common types of HAIs caused by CRE. Like Hospital X's CRE outbreak, this outbreak in Taiwan was reportedly terminated only once the hospital used EtO sterilization to process the implicated ureteroscope[9,25,44].

Sorin *et al*[45] (2001) report that 18 patients were either colonized or infected with imipenem-resistant *P. aeruginosa* (IRPA), an infectious strain of bacteria that, while of the *Pseudomonadaceae*, not *Enterobacteriaceae*, family and therefore not CRE, is a related superbug that is resistant to carbapenems. (Noted previously, imipenem is a type of carbapenem antibiotic). This outbreak was reportedly due to the improper connection of an automated reprocessing device to the bronchoscope's suction channel, presumably precluding the endoscope's effective reprocessing. Sorin *et al*[45]'s (2001) findings suggest that contaminated bronchoscopes, too, like GI endoscopes and urological equipment, pose a risk of transmission of multidrug-resistant gram-negative bacteria, like IRPA and CRE. Whether other types of GI endoscopes featuring an exposed elevator wire channel, such as those used during endoscopic ultrasonography (or, "EUS"), might also be difficult to clean and pose an increased risk of CRE transmission is unclear, but possible[46]. Based in part on a review of Sorin *et al*[45]'s (2001) report, Muscarella (2004) found that environmental surfaces including tap water may, too, be reservoirs for antibiotic-resistant strains of gram-negative bacteria[47].

High-level disinfection: Does it rapidly destroy CRE and related superbugs?

An important question to address - in response to the CDC's report in MMWR that Hospital X's outbreak of CRE (and the CRE outbreak reported by Chang *et al*[44] [2013] seemingly stopped after this hospital replaced (automated) high-level disinfection of its ERCP endoscopes with EtO sterilization[25] - is whether high-level disinfection can indeed destroy CRE and their related superbugs. A number of studies and published data address this concern. Aumeran *et al*[21] (2010), for example, report that a peracetic acid-based high-level disinfectant (sold in Europe) was tested and verified to be "fully effective" against a multidrug-resistant strain of *K. pneumoniae*. Additionally, several intermediate-level disinfectants registered with the Environmental Protection Agency (EPA) in the United States are specifically labeled to destroy CRE within 1 or 2 min[48,49]. Whereas intermediate-level disinfectants are tuberculocidal, high-level disinfectants are even more robust, being both tuberculocidal and, during longer exposure times, sporicidal. It is therefore reasonable to conclude that all high-level disinfectants cleared by the FDA destroy virtually every strain of CRE even more rapidly than intermediate-level disinfectants.

Moreover, not only gram-negative superbugs like CRE, but also such gram-positive superbugs as MRSA and VRE are reported to be no more resistant to intermediate-level disinfection (*i.e.*, their destruction does not require a longer time of exposure to the disinfectant) than their antibiotic-*susceptible* counterparts, carbapenem-susceptible *Enterobacteriaceae*, "MSSA" and "VSE," respectively[48,49]. While some of the published data are conflicting, other reports suggest that the development of antibiotic resistance by bacteria does not appear to be correlated with an increased resistance to disinfectants[50,51]. In short, published data suggest that high-level disinfection rapidly kills CRE and their related superbugs. Moreover, to date, there are insufficient data to conclude that cleaning following by high-level disinfection (and thorough drying and proper storage) of GI endoscopes, especially ERCP endoscopes, is inadequate and unsafe for the prevention of transmission of CRE[30,32] (provided the endoscope's design facilitates contact of the disinfectant with all of the instrument's potentially contaminated surfaces), or that EtO sterilization (or a comparable low-temperature sterilization technology) is required to prevent CRE transmissions *via* a GI endoscope[30] (both the suggestions of the CDC's report in MMWR[25] in 2014 and Chang *et al*[44]'s [2013] report notwithstanding).

The CDC's, SGNA's and ASGE's recommendations for reprocessing GI endoscopes contaminated with CRE

The CDC reported that Hospital X's aforementioned outbreak of CRE in 2013 was terminated once the hospital replaced automated high-level disinfection of its ERCP endoscopes with EtO sterilization[25,31]. According to one hospital official, as a precaution, Hospital X "moved to (ethylene oxide) gas sterilization for these particular scopes, which exceeds the manufacturer's recommended cleaning and disinfectant guidelines to ensure no other patients are at risk"[29]. No matter, the CDC does not recommend the EtO sterilization of all ERCP endoscopes, stating in 2014 that: "At this time, CDC recommends facilities reprocess endoscopes as directed by the manufacturer; however, this is a focus of the ongoing assessments. CDC is not recommending a wholesale switch to sterilization; however, facilities should review their endoscope reprocessing practices to ensure all manufacturers' reprocessing recommendations are followed exactly. Any reprocessing recommendations, including sterilization with ethylene oxide (if recommended), would be validated by the manufacturer"[30].

Consistent with the CDC's stance, the Society for Gastroenterology Nurses and Associates (SGNA) and the American Society for Gastrointestinal Endoscopy (ASGE) issued a joint statement in 2014, in response to Hospital X's CRE outbreak the previous year[32]. In that statement both organizations concluded that: "If ERCP-related transmission of CRE is suspected, reprocessing and preventative maintenance procedures for ERCP endoscopes should be evaluated in consultation with the manufacturer of the endoscope and automated endoscope reprocessor, if used"[32]. Their statement adds the following directive: "Please remember to follow the manufacturer's safety and reprocessing instructions, and don't hesitate to contact your manufacturer's representative for any questions related to equipment reprocessing"[32]. In short, neither ASGE nor SGNA currently recommends that endoscope reprocessing practices be revised, upgraded or changed significantly. These practices, which

define the current standard of care, include high-level disinfection (preceded by manual cleaning) for the prevention of CRE transmissions during GI endoscopy and other flexible endoscopic procedures.

Some unresolved issues associated with Hospital X's CRE outbreak in 2013

Community-acquired CRE infections? A number of issues surrounding Hospital X's outbreak of CRE remain unresolved, including its precise cause(s). In addition to Hospital X's 38 exposed patients who were found to be either colonized (n = 28) or infected (n = 10) with CRE following ERCP, the CDC reported that another 6 patients (44 patients, in total) were also similarly infected or colonized with CRE in northeastern Illinois (United States) between January and December, 2013[25,31], causing this outbreak of CRE to be the largest in United States history, although none of these 6 other patients reportedly received care at Hospital X. Whether any of these 6 infected or colonized patients had been in direct or indirect contact with one or more of Hospital X's 38 affected patients, demonstrating, possibly, community-associated transmission of CRE, is unclear, but important to evaluate.

EtO sterilization: As previously noted, the CDC reported (in MMWR) that no new cases of CRE transmissions due to a contaminated ERCP endoscope were identified once Hospital X replaced the automated high-level disinfection of its ERCP endoscopes (using an AER) with EtO sterilization[25,29,31]. Whether this low-temperature sterilization process is sufficiently robust to overcome, possibly, the hindrances that the ERCP endoscope's complex physical design reportedly poses to successful reprocessing, or that some other confounding factor altogether was responsible instead for stopping Hospital X's CRE outbreak, requires more confirmatory data. (No matter, EtO sterilization may be used by a healthcare facility as one of several "bundled" interventions concomitantly implemented to terminate a CRE outbreak. Circumspection is recommended, however, as no device that uses EtO gas has been cleared by the FDA with the specific intended use to sterilize ERCP endoscopes). Also previously noted, Bernie *et al*[9] (1983) recommended, and Chang *et al*[44] (2013) implemented, EtO sterilization to prevent transmission of the HBV *via* a GI endoscope and of CRE *via* a ureteroscope, respectively. The conclusion suggested by the CDC[25] that the ERCP endoscope's complex physical design - including that of its forceps elevator (Figure 1B), which presumably hindered reprocessing - was a primary contributor to, if not the cause of, Hospital X's CRE outbreak also requires more confirmatory data.

CRE-contaminated water? Hospital X's use of EtO sterilization for the apparent termination of its CRE outbreak in 2013 intriguingly raises another unresolved issue: that, possibly, a hitherto overlooked factor might have contributed to or caused this outbreak - namely, one that Muscarella[2] (2010) has previously discussed as a risk factor for other, similar instances of transmissions of multidrug-resistant bacteria during GI endoscopy: contaminated tap water. Because the CDC's report in MMWR does not discuss whether Hospital X's environmental surfaces, including its tap water or the AER's rinse water (or, too, the AER's internal components and water filters), were microbiologically sampled for contamination with CRE[25], there remains the possibility that the water supply (or another related moist or wet environmental surface, such as a sink) used by Hospital X to rinse its ERCP endoscopes following high-level disinfection might have been contaminated with the outbreak's strain of CRE (*i.e.*, NDM-1-producing *E. coli*). Indeed, contaminated rinse water used during endoscope reprocessing, coupled with inadequate drying of the ERCP endoscope's internal channels after terminal water rinsing, is a commonly documented contributor to bacterial transmissions *via* contaminated GI endoscopes[2,7,8,11,12]. For certain, in addition to a human's GI tract, water (and soil) is a documented reservoir of CRE[2,44,45,51-54]. That another unrecognized factor altogether may have been the primary cause of (or a contributor to) Hospital X's CRE outbreak also remains plausible. [Note: CMS's inspection report of Hospital X[31] raises the possibility, in addition to the two strains of CRE that the CDC recovered from one of Hospital X's contaminated ERCP endoscope (*i.e.*, NDM-producing E. coli and KPC-producing *K. pneumonia*), that a third strain of CRE - namely, NDM-producing *K. pneumoniae* - might also have infected or colonized at least one patient (*i.e.*, "Patient #10"[31]) who underwent ERCP during the time of Hospital X's outbreak and who subsequently expired].

Faulty reprocessing? According to the CMS's aforementioned health inspection report published in 2014, in the aftermath of Hospital X's CRE outbreak, the manufacturer of the implicated ERCP endoscope model asserts that Hospital X did not clean its ERCP endoscopes as their labeling instructs[31]. First, instead of it using the cleaning brushes specifically designed, validated and "highly recommended" (but not necessarily required) by the ERCP endoscope's manufacturer, this inspection report states that Hospital X used another manufacturer's brushes to clean its ERCP endoscopes (*i.e.*, a claimed "off-label" practice). Second, this inspection report also indicates that Hospital X used an enzymatic detergent to clean the implicated ERCP endoscopes that had not been "approved" by the endoscope's manufacturer and confirmed to be compatible with the materials used in the endoscope's construction (*i.e.*, another claimed "off-label" practice). The extent to which Hospital X's failure to use either the specific type of cleaning brushes or a detergent recommended or approved by the ERCP endoscope's manufacturer, respectively, contributed to Hospital X's CRE outbreak is unclear.

Patient mortality linked to GI endoscopy: Of Hospital X's 38 patients who were exposed to the outbreak strain of CRE while undergoing ERCP in 2013, 28 patients became colonized and 10 infected, with two of these 10 infected patients subsequently dying[31]. Whether the outbreak's strain of CRE was the primary cause of these deaths, only contributed to them, or was incidental is subject to professional judgment and both clinical data and

debate. Whichever, the fact that two of Hospital X's 10 CRE-infected patients died following their exposure to one of three contaminated ERCP endoscopes is an additional testament, not only to GI endoscopy now being a confirmed risk factor for CRE infection, but also to the importance of reprocessing every one of the GI endoscope's potentially contaminated surfaces and areas following its use, lest the instrument remain contaminated and transmit CRE or their related superbugs, with associated morbidity and mortality.

RECOMMENDATIONS AND GUIDANCE

Several recommendations are provided to prevent transmissions of CRE and their related superbugs during GI endoscopy (and other types of flexible endoscopic procedures). For example, strict adherence to the cleaning instructions provided by the GI endoscope's (or the AER's) manufacturer, especially the instructions for brushing the area around, near and behind the forceps elevator located at the distal end of the ERCP endoscope (Figure 1B), is emphasized. More frequent monitoring of reprocessing staffers to verify the proper reprocessing of GI endoscopes, particularly ERCP endoscopes, is also recommended. High-level disinfection, whether achieved using a FDA-cleared aldehyde-based disinfectant or an oxizing agent, remains the recommended standard of care and can be expected to destroy CRE rapidly. Use of EtO sterilization for processing GI endoscopes, in lieu of manual or automated high-level disinfection, is neither contraindicated nor required (except, possibly, as part of an initial and "bundled" response to terminate a CRE outbreak)[30]. Enhanced surveillance designed to identify CRE infections and colonizations quickly and proactively, such as the screening of patients (*e.g.*, rectal or perianal swabbing to detect gastrointestinal carriage of CRE) upon admission, warrants consideration. A number of other interventions intended to prevent CRE transmission are provided below. Review of other published articles that provide additional guidance for the prevention of transmisson of all types of infectious agents during GI endoscopy is encouraged[3-6,14,47,55-58].

Transmission-based precautions

Standard precautions are important to the prevention of CRE transmissions in the GI endoscopic setting. For example: (1) practice proper hand-hygiene etiquette consistent with the CDC's guidelines[59]; (2) don personal protective equipment (PPE), wearing gloves, gowns, and a face mask, as needed[15]; and (3) in addition to high-level disinfecting (or sterilizing) GI endoscopes (and other *semi-critical* devices), sterilize reusable critical items, such as reusable biopsy forceps, and regularly clean and disinfect (using a low- or intermediate-level disinfectant) both non-critical devices, such as stethoscopes, and environment surfaces, such as countertops, as prescribed by the CDC's guidelines (*i.e.*, ideally, using an EPA-registered, hospital-grade disinfectant labeled to rapidly kill CRE for those surfaces potentially contaminated with these superbugs)[60]. Moreover, the prevention of CRE transmissions will also likely require the implementation of *Contact Precautions* for patients infected or colonized with CRE, cohorting these patients and the healthcare staff treating them as deemed necessary[25].

Endoscope reprocessing

A number of recommended practices for the proper reprocessing of GI endoscopes that are based on this article's findings are provided in Table 3. Recommended practices include placing emphasis on the cleaning and complete brushing (prior to high-level disinfection or sterilization) of the area of the ERCP endoscope near, around and behind its forceps elevator (Figure 1B), as well as flushing this endoscope's elevator wire channel (if it is exposed and unsealed) with detergent using a procedure validated for effectiveness. The use of cleaning accessories, including brushes and detergents, recommended and validated by the GI endoscope's manufacturer may prove to be important.

Other recommendations

Efforts by healthcare professionals to educate themselves on the epidemiology of CRE and related superbugs; their modes of transmission; their common sources and reservoirs; and their mechanisms of resistance to carbapenems and other antibiotics are encouraged as part of a broad program to prevent CRE transmissions during GI endoscopy. Better stewardship and the reduced or restricted (and more judicious) use of antimicrobial drugs for the treatment of patients infected with CRE and their related superbugs is recommended as a corrective action to slow, if not to prevent, the development of antibiotic-resistant infections. And, of course, failure to adhere to strict aseptic techniques during the administration of *iv* medications used during GI endoscopy poses a significant risk of viral (and bacterial) transmissions[57].

Attention by manufacturers of GI endoscopes to perform, in addition to performance testing and other regulatory requirements, enhanced risk assessments and other quality, safety and design-control strategies that assess the likelihood of CRE transmissions; evaluate the potential impact of these transmissions (which can be significant) on patient safety; mitigate further the risk of these transmissions (and other patient harms) during GI endoscopy - for example, by enhancing endoscope designs to optimize thorough cleaning and complete reprocessing; and, by updating the endoscope's reprocessing manuals to provide even more detailed cleaning instructions using even better performing cleaning brushes and detergents; and validate the success of each corrective and preventive action (or mitigation) developed and employed to prevent these transmissions *via* a GI endoscope is encouraged. Indeed, because of the possibility that the FDA's regulatory oversight of manufacturers of GI endoscopes and related instrumentation - like closer scrutiny, too, of the infection-control and endoscope-reprocessing practices of surveyed GI endoscopy departments by healthcare accrediting organizations and state health departments - may increase as a consequence of

several recently disclosed CRE outbreaks (see text, above, and Table 4), it may prove prudent for both manufacturers and GI endoscopy departments alike to place enhanced focus on quality activities specifically designed to prevent CRE transmissions during GI endoscopy. Not to be overlooked is the importance to public health of trending and surveillance activities, and, respectfully, of both manufacturers and healthcare professionals filing prompt and complete reports about an identified CRE outbreak (linked to a medical device) with the FDA *via* its MAUDE database (Table 4).

CONCLUSION

This article answers several questions posed in Table 1 about CRE, their related superbugs, and the risk of transmission of these multidrug-resistant bacteria during GI endoscopy and other flexible endoscopic procedures. Not only are they an emerging public health threat (Table 2) both globally and in the Unites States, but this article identified GI endoscopy to be a risk factor for infection and colonization with CRE and their related superbugs (as well as with other types of antibiotic-resistant bacteria; antibiotic-susceptible bacteria, too; and other infectious agents, including viruses), with associated morbidity and mortality[33]. Strict adherence to infection control in the GI endoscopic setting is necessary to ensure patient safety and prevent disease transmission[33]. To date, high-level disinfection appears sufficient to prevent a GI endoscope from transmitting CRE and their related superbugs (provided the disinfectant contacts all of the endoscope's surfaces contaminated with CRE). Nonetheless, EtO sterilization of ERCP endoscopes may be employed prophylactically or once CRE transmissions have been confirmed (unless it is contraindicated by the GI endoscope's manufacturer), although the effectiveness of this low-temperature sterilization process for the prevention of CRE transmission is based on clinical data and reports, not necessarily rigorous simulated-in use validation studies that have been reviewed by the FDA. Special attention is placed on healthcare staff assuring thorough cleaning of the ERCP endoscope (Figure 1B), especially the area around, behind and near its forceps elevator (and, if exposed, the flushing of its elevator wire channel with a detergent validated for effectiveness and materials' compatibility). Additional recommendations are provided in Table 3.

Postscript

At the time this article was published in October, 2014, the CDC had just published a more comprehensive review of its investigation of Hospital X than it provided in MMWR earlier in January, 2014[25,69]. (The reader's review of this more recent CDC report is recommended). Moreover, on October 9, 2014, the University of Pittsburgh Medical Center (UPMC) reported that after having identified an "uptick" of antibiotic-resistant infections (*i.e.*, an outbreak of CRE) in patients who underwent ERCP in 2012, the hospital changed its practices from high-level disinfection of ERCP endoscopes to ethylene oxide gas (EtO) sterilization[70]. According to UPMC, the "normal process" (*i.e.*, high-level disinfection) "failed to eliminate all bacteria" (presumably, from the ERCP endoscope's elevator wire channel)[70]. Whether the hospital and/or one or more manufacturers (*i.e.*, of the ERCP endoscope and, if one were used, the automated endoscope reprocessor, or AER) filed a report with the FDA documenting these CRE infections in the Agency's MAUDE database, like whether this outbreak at UPMC is one of the MAUDE reports listed in Table 4, is unclear. [A related, timely, and closing note: In response to its current outbreak in certain regions of the world, patient-to-patient transmission of the Ebola virus *via* properly disinfected or sterilized reusable medical instrumentation has not been reported].

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MINIREVIEWS

Endoscopic management of foreign bodies in the upper gastrointestinal tract: A review

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Abstract

Foreign body ingestion is a common condition, especially among children who represent 80% of these emergencies. The most frequently ingested foreign bodies in children are coins, toys, magnets and batteries. Most foreign body ingestions in adults occur while eating, leading to either bone or meat bolus impaction. Flexible endoscopy is the therapeutic method of choice for relieving food impaction and removing true foreign bodies with a success rate of over 95% and with minimal complications. This review describes a comprehensive approach towards patients presenting with foreign body ingestion. Recommendations are based on a review of the literature and extensive personal experience.

Key words: Foreign body; Endoscopic management; Esophageal stricture; Food bolus impaction; True foreign body

Core tip: It is vitally important for physicians to recognize the current and most common types of upper gastrointestinal foreign bodies presented today. Knowledge regarding the modern advanced methods and techniques available when treating patients with foreign bodies will keep the success rate of recovery above 96%.

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INTRODUCTION

An estimated 1500 people in the United States die annually from foreign bodies in the upper-gastrointestinal (GI) tract[1]. Ingestion of foreign bodies is common, especially, among children who represent 80% of these emergencies. Most foreign body ingestions in children, are coins, toys, magnets and batteries[2-4]. Most foreign body ingestions in adults are related to eating, leading to either bone or meat bolus impaction[5]. Patients who purposely swallow a true foreign body (nonfood object) typically are younger and more often male; associated psychiatric illness and/or drug abuse are common[1,6]. Most ingested foreign bodies (80%-90%) pass spontaneously. However, approximately 10%-20% of foreign bodies necessitate an endoscopic procedure, whereas, less than 1% require operation[6-10]. This review emphasizes etiology, diagnosis, therapy and prognosis of upper GI foreign bodies based on a literature review and personal observations.

EPIDEMIOLOGY

The types of ingested objects vary with patient age[2-4,11]. Coins accounted for 66% of the upper GI foreign bodies found in patients less than 10 years of age; in contrast,

food boluses account for 60% of upper GI foreign bodies in those over 11 years old[5] (Table 1), A food bolus impaction, in the adult patients, if often due to an underlying structural abnormality, such as an esophageal web, ring, a benign or malignant stricture or eosinophilic esophagitis (Table 1)[8,9,12,13]. Roura *et al*[5] noted that 99% of ingested foreign bodies, in their series of 242 patients, become lodged in the upper GI tract; these foreign bodies were found in the pharynx in 39 patients, in the esophagus in 181 patients, in the stomach in 19 patients and in the small intestine in 3 patients.

Table 1 Classifications of foreign bodies

Blunt objects
Round objects: coin, button, toy
Battery
Sharp-pointed objects
Fine objects: needle, toothpick, bone, safety-pin
Sharp irregular objects: partial denture, razor blade
Long objects
Soft objects: string, cord
Hard objects: toothbrush, spoon, screwdriver, ballpoint pen
Food bolus impaction
Bezoar
Objects containing poisons
Button battery
Narcotic body packet

Table 2 Indications for foreign body removal

Emergent indications
Sharp-pointed objects
Needle, toothpick, bone, safety-pin, partial denture, razor blade, medication blister packs
Object inducing esophageal obstruction
Food bolus
Object including poisons
Button battery
Non Emergent Indications (blunt rounded objects)
Coin, button, small toy

PATHOPHYSIOLOGY

The majority (80%-90%) of foreign bodies and food impactions will pass spontaneously. Ten to twenty percent of gastrointestinal foreign bodies will require endoscopic intervention. Few patients who ingest foreign bodies require surgery[6-10]. Impaction, perforation, or obstruction most often occurs at areas of acute angulations or physiologic narrowing. Potential sites for blocking include the cricopharyngeus muscle or upper sphincter, aortic arch, left main stem bronchus, gastroesophageal junction or lower sphincter, pylorus, duodenal sweep, ileocecal valve, and anus. Foreign bodies and food impactions in the esophagus have the highest incidence of complications with the complication rate directly proportional to the dwell time in the esophagus[14]. Perforation is most common with sharp objects, and ranges from 15%-35%[6,15].

Materials retained in the upper GI tract generally fall into two categories, namely, a food bolus impaction and a true foreign body[15,16]. Classifications for foreign bodies, which define anatomic region and shape, are important for defining optimal therapy (Table 1). Sharp-pointed objects, food bolus impaction, and button batteries may lead to upper GI tract perforation, obstruction or bleeding, thereby necessitating earlier intervention (Table 2).

DIAGNOSIS

The diagnosis is often apparent from the patient's history. The patient may report a sudden onset of dysphagia while eating, often accompanied by chest pain or odynophagia and an inability to handle secretions. When children are unable to provide a history, a sudden refusal to eat, drooling, or respiratory symptoms such as coughing or wheezing due to aspiration should alert the physician to suspect foreign body ingestion. A careful physical examination should assess for signs of perforation such as subcutaneous emphysema or peritoneal signs. Drooling suggests complete esophageal obstruction.

Plain radiography may show the foreign body; perforation is suggested by subcutaneous air, pneumomediastinum, or pleural effusion. Barium studies also have a very low yield; gastrografin is not recommended in the obstructed esophagus because it is hypertonic and can lead to pulmonary edema if aspirated[14]. CT scanning is superior to plain radiography and identifies the foreign bodies in 70%-100% of patients[17-19].

Urgent endoscopy is indicated when there is respiratory distress, airway compromise, or when complete obstruction is suspected because a patient cannot handle internal secretions. Endoscopic diagnosis and therapeutic removal can be performed at the same time[16].

TREATMENT

Timing

Once foreign body ingestion is diagnosed, the physician must decide whether intervention is necessary, what degree of urgency is merited, and what the optimal modality of intervention might be. The timing of endoscopic intervention is dictated by the perceived risks of aspiration and/or perforation. Patients with sharp objects and disk batteries lodged in the esophagus require urgent endoscopic intervention. Urgent intervention is likewise needed for foreign bodies, such as food impactions, causing obstruction and the inability to manage secretions (Table 2). Those without evidence of high-grade obstruction, or acute distress, can be handled less urgently as spontaneous passage may occur. However, no foreign object or food bolus impaction should be allowed to remain in the esophagus beyond 24-h after presentation[20].

SEDATION

Conscious sedation is adequate for the majority of adult patients. General anesthesia with endotracheal intubation

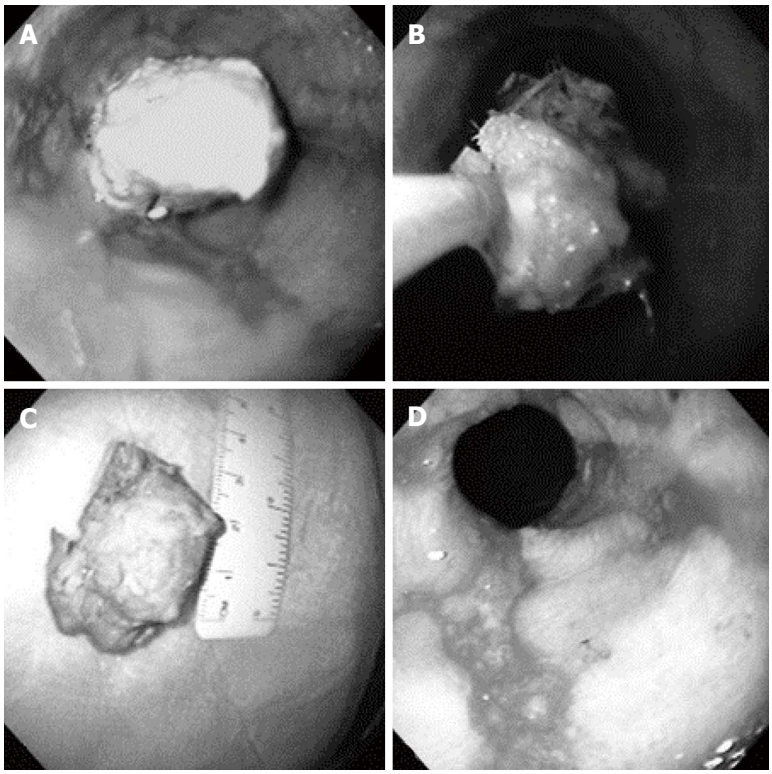

Figure 1 The photographs (A) show a piece of meat lodged at a narrowed gastroesophageal ring; the meat was removed with the snare (B and C). The photo (D) shows the ring after extraction with esophagitis; the narrowing was successfully dilated.

will give full protection of the airway and is ideal in most pediatric patients. Furthermore, general anesthesia with endotracheal intubation is best for the uncooperative psychotic patient and those who have ingested multiple objects, thereby, prolonging extrication time.

EQUIPMENT

Endoscopes

Endoscopists should be available and familiar with a wide range of tools for removing foreign bodies. A flexible endoscope is the diagnostic as well as therapeutic method of choice for food impaction and true foreign bodies with success rates of greater than 95% and complication rates of 0%-5%[7,8,16]. The push-and-pull double-balloon enteroscopy may be successful for removal of entrapped capsules from the small intestine[21-25].

Retrieval devices

Retrieval tools include grasping forceps, polypectomy snares, Dormier-type stone retrieval baskets, retrieval snare net, transparent cap-fitting device (used for endoscopic mucosal resection)[26] and overtube[27,28]. A retractable latex-rubber condom-typed hood is effective for delivering objects across the sphincter and for preventing mural injury from sharp or pointed edged objects[29]. An overtube protects the airway and facilitates passage of the endoscope during removal of multiple objects or piecemeal removal of a food impaction[27,28]. An overtube also protects the esophageal or gastroesophageal junction mucosa from laceration during retrieval of sharp objects[28].

Food bolus impaction

A food bolus impaction is usually the result of an underlying structural abnormality, such as a web, ring or stricture of the esophagus (Figure 1, Tables 1 and 2)[30]. An esophageal food bolus impaction often contains chewed meat lodged at one of these narrowed sites. Adult patients who develop food impaction have underlying esophageal pathology in 88% to 97% of patients[31]. Esophageal obstruction by a food bolus is the most common type of foreign-body ingestion complication in adults[32]. The obstruction is often complete and may be associated with increased salivation, the inability to swallow liquids, substernal pain, and aspiration[30]. Thus, successful endoscopic treatment of food impaction as well as the underlying pathologic lesion is essential.

Using a snare or snare basket, a food bolus can be retrieved in one piece or by piecemeal extraction (Figure 1) or reduced in volume allowing it to pass spontaneously. The food may be successfully pushed into the stomach after it is cut into small pieces by a snare[31]. This technique involves bypassing the esophageal narrowing with the endoscope, while assessing the cause of the obstruction. After the endoscope is passed into the stomach, the food may be gently pushed distally. Forceful blind pushing with the endoscope is dangerous. Similarly, advancing retrieval devices or dilators blindly beyond the impaction invites complications. If food is extracted through the mouth either in one piece or piecemeal (Figure 1), use of

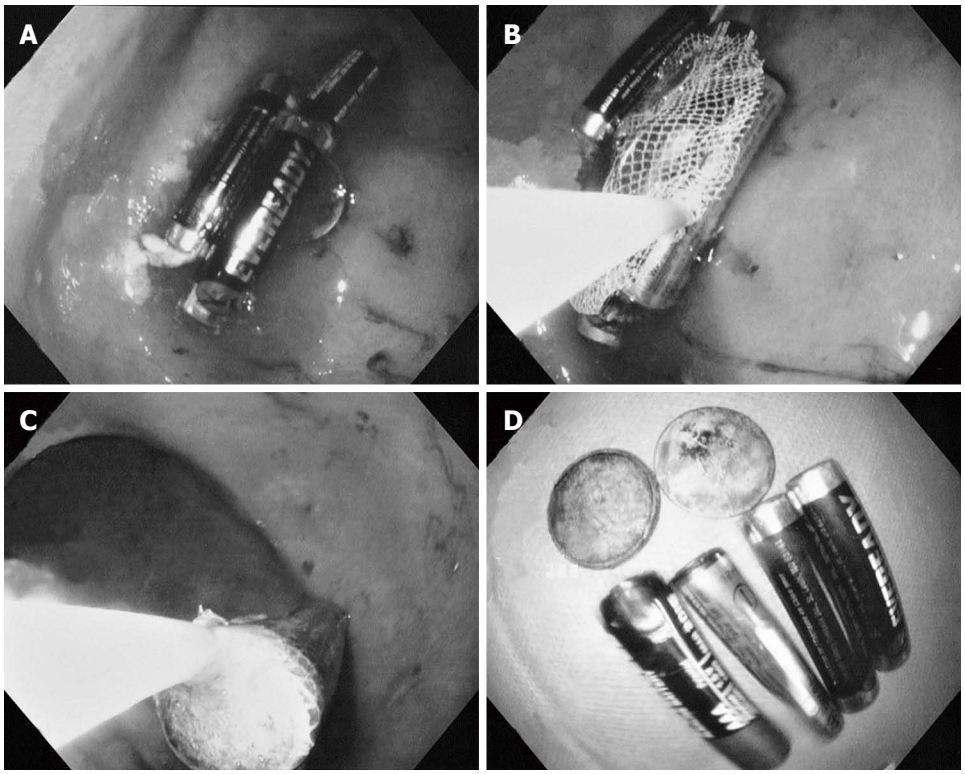

Figure 2 A 54-year-old woman with history of psychiatric illness swallowed four AA batteries and two button batteries (A). All these batteries in the stomach were removed using a snare net (B) one by one (C and D). Note the multiple erosions and shallow ulcers caused by button batteries (A, B and C).

an overtube to protect the airway against aspiration may be employed[27,31]. A stricture can be treated with a balloon dilator after successful extraction or passage of an impacted food bolus distally.

Blunt object

The most common blunt foreign bodies are coins ingested by children (Tables 1 and 2). Approximately 30% of coins will pass from the esophagus into the stomach within 24 h[33]. If the object has passed into the stomach and is less than 2 cm in size, it will usually pass through the entire gastrointestinal tract without difficulty. These can be retrieved using a retrieval snare net if objects fail to pass beyond the stomach by 3 to 4 wk[7].

Button or small disk batteries

Button or small disk batteries are found in watches, hearing aids, calculators and other electronic devices. If both poles of the battery come into contact with the mucosa, electrical conduction may result in corrosive injury, necrosis and perforation (Tables 1 and 2, Figure 2). Furthermore, these agents contain either metallic salts (mercuric oxide, silver oxide, zinc oxide, or lithium oxide) or alkaline fluids (sodium or potassium hydroxide), which may leak into the gastrointestinal lumen and cause necrosis. After radiographic documentation, batteries lodged in the esophagus or stomach should be emergently removed. Use of a retrieval snare net or a stone retrieval basket is most often successful (Figure 2)[26]. Surgical management is recommended if severe abdominal pain develops or if the battery fails to pass in 72 h[34,35].

Sharp-pointed object

Common sharp pointed foreign bodies include bones, toothpicks, needles, safety pins, nails, dental appliances and medication blister packs (Tables 1 and 2, Figure 3). They should be removed, if possible, before they pass through the stomach, as 15%-35% of these objects will perforate the intestine, usually, near the ileocecal valve[6,15]. Budnick *et al*[36] reported 8176 toothpick-related injuries in the United States from 1979 to 1982; this is a rate of 3.6 per 100000 person-years. Patients often do not remember swallowing a toothpick and imaging studies demonstrate the presence of a toothpick in only 14% of patients[36-40]. Sharp foreign body ingestion, such as bones and toothpicks, can be dangerous by causing airway compromise, bowel perforation or penetration[41,42], aortic or tracheal fistulae[43,44], or cardiac tamponade (Tables 1 and 2)[45,46]. Ingested sharp-pointed objects have the highest rates of perforation, which may be 35%[2,46]. Sharp objects within the esophagus should be urgently removed endoscopically. Surgical intervention is indicated if the patient develops symptoms of perforation or if the ingested sharp object fails to progress within 72 h after ingestion[6]. Medication blister packs can cause bleeding or perforation of the esophagus[47]. They can be removed by a snare net. For removal of sharp and pointed objects, use of an overtube or a retractable latex-rubber condom-type hood is recommended. One should always remember that advancing points puncture, whereas, trailing ones do not.

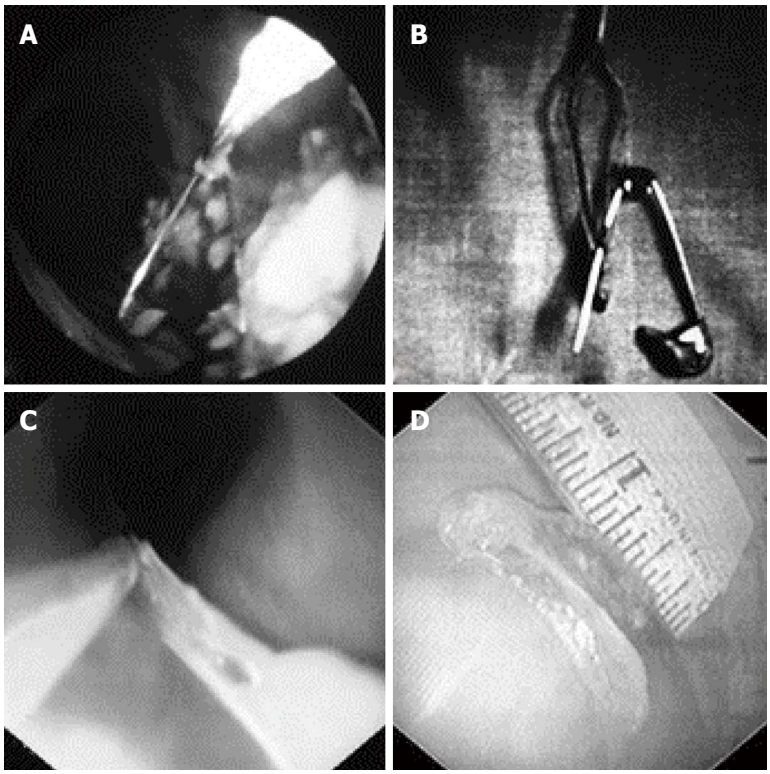

Figure 3 The top photos (A and B) show a swallowed safety-pin in the stomach, removed with the gallstone retrieval basket. The lower photos (C and D) show a swallowed cat fish bone stuck in the proximal esophagus. The sharper edge was dislodged from the esophageal wall with a snare (C), and removed (D).

Pointed objects should always be removed such that the pointed end is trailing as done in a safety pin (Figure 3A and B) or fish bone removal[7,16]. These objects can also be retrieved using a polypectomy snare (Figure 3C and D). Surgical removal should be considered if endoscopic retrieval is impossible and the object has not moved in 72 h or if it is advancing with a pointed end[6,14].

Long object

Objects greater than 5 cm in length, such as pens, toothbrushes, spoons and cutlery, usually become lodged in the duodenal sweep, requiring removal. This can generally be accomplished with a polypectomy snare (Figure 4A and B). An overtube may be required to protect the airway. Long objects like a large metal spoon lodged in the duodenum need surgical removal when endoscopic efforts fail (Figure 4C and D).

Bezoar

Bezoars are concretions of foreign material that become fixed in the stomach and occasionally the duodenum. They may be of vegetable origin (phytobezoar), or consist of ingested hair (trichobezoar). Patients will present with a chronic history of vomiting, dyspepsia, abdominal discomfort or weight loss. A barium upper gastrointestinal series may provide diagnosis, but diagnostic endoscopy may also be therapeutic.

Treatment of phytobezoars using enzymatic digestion has occasionally been effective. This has been particularly true with the use of cellulase, which will digest vegetable matter. Large bezoars may be fixed to the gastric wall and difficult to manipulate endoscopically. Accessories such as snares and stone baskets or the lithotripter are useful for fragmenting and removing large portions of the bezoars[16]. Some bezoars, particularly trichobezoars, may be so large and fixed that prompt laparotomy is the most efficacious therapy[48].

Narcotic body packets

Cocaine may be smuggled by swallowing packets containing cocaine inside protective coverings, such as condoms (Table 1). The packets can usually be seen on plain abdominal films. Endoscopic retrieval of these packets is contraindicated for fear of puncture. The packets typically contain 3-5 gm of cocaine. Inpatient observation is recommended. Surgery is indicated for failure of the packets to progress, signs of intestinal obstruction, or clinical finding suggesting rupture[49].

Small-bowel foreign bodies

Removal of retained endoscopy capsules, coins and migrated stents has been achieved using single- or double-balloon enteroscopy[21-25]. Use of balloon enteroscopy for foreign body removal should be decided by the type of foreign body, availability of enteroscopy accessories, and duration of the procedure.

CONCLUSION

Most upper GI foreign bodies in adults are related to

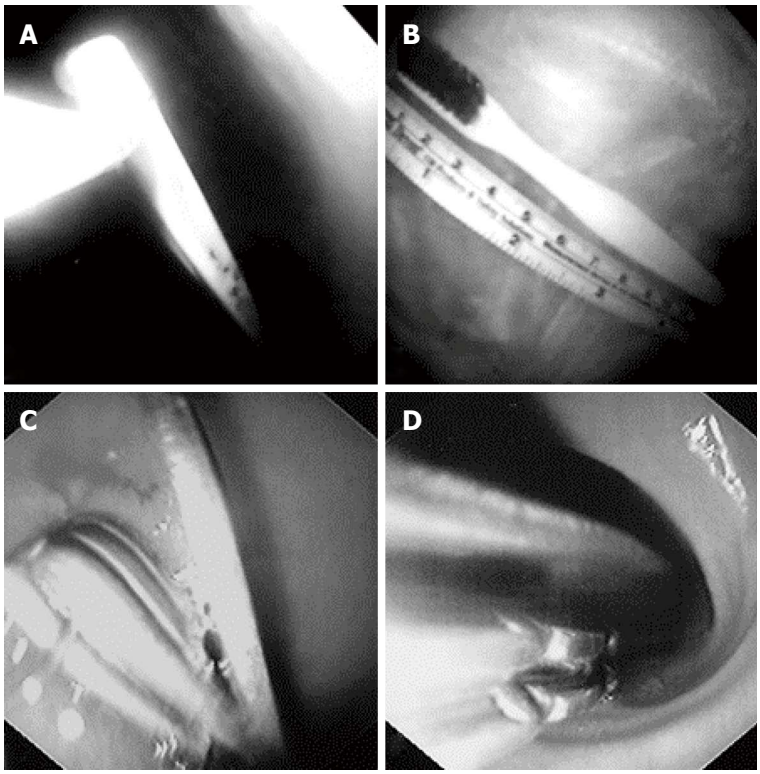

Figure 4 The top photo (A and B) shows a toothbrush being removed from the stomach with a snare. The lower photos (C and D) show several large metal spoons in the gastric antrum extending into the duodenal bulb; these could not be removed endoscopically. Successful laparoscopic surgery was performed.

food bolus impaction with meat. Patients who swallow a true foreign body typically are younger, more often male, and often have significant psychiatric illness and/or drug abuse. A variety of endoscopic techniques and instruments are indicated for different situations. Flexible endoscopic treatment is a safe and reliable procedure for a skilled endoscopist, with a high success rate, low morbidity, and no mortality[6,16].

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Role of preoperative tracheobronchoscopy in newborns with esophageal atresia: A review

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Abstract

Preoperative tracheobronchoscopy (TBS) in the diagnostic assessment of newborns affected by esophageal atresia (EA) was described in 1981. Nevertheless, the value of the procedure is actually much debated; only a few studies have clearly explored the advantages of TBS and this procedure is not yet routinely included in the diagnostic and therapeutic assessment in many international pediatric surgery settings. Routine preoperative TBS is a safe procedure that enables the accurate examination of the tracheobronchial tree, the visualization of tracheoesophageal fistula and the diagnosis of tracheomalacia or associated respiratory anomalies. When a distal fistula is found, its occlusion with a Fogarty balloon catheter improves mechanical ventilation and facilitates surgical repair. This review provides a detailed overview on the use of TBS in newborns with EA, focusing on technical aspects, anesthesiological management, indications and limits. The benefits and risks of the procedure are also compared with alternative diagnostic tools, such as an esophageal contrast study, computed tomography scan and ultrasound.

Key words: Computed tomography scan; Esophageal atresia; Newborns; Tracheobronchoscopy; Tracheoesophageal fistula; Tracheomalacia

Core tip: Despite preliminary tracheobronchoscopy (TBS) in the management of newborns affected by esophageal atresia (EA) being described in 1981, only a few studies have clearly explored the advantages of TBS in the subsequent years and this procedure is still not routinely part of the diagnostic and surgical assessment in many international pediatric surgery centers. This review provides a detailed overview on the use of TBS in newborns with EA, focusing on technical and anesthesiological aspects, benefits and risks of this procedure. TBS is also compared with alternative diagnostic tools, such as an esophageal contrast study, computed tomography scan and ultrasound.

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INTRODUCTION

More than thirty years ago in 1981, Benjamin first highlighted the importance of preliminary tracheobronchoscopy (TBS) in the management of 152 newborns affected by esophageal atresia (EA), enabling an accurate examination of the tracheobronchial tree and the diagnosis of tracheomalacia or associated upper respiratory anomalies[1]. Nevertheless, in subsequent years, only a few studies clearly explored the advantages of TBS in these patients and this procedure is not yet routinely included in the diagnostic and surgical assessment in many pediatric surgery centers all over the world[2,3]. This review provides a detailed overview on the use of TBS in newborns with EA, focusing on technical and anesthesiological aspects and comparing benefits and risks of the procedure with alternative diagnostic tools.

BACKGROUND

Multicenter studies on diagnostic assessment and operative management of newborns with EA are lacking and only scant data on the use of TBS are available (Table 1). Lal *et al*[4] reported an online-based survey sent to all members of the International Pediatric Endosurgery Group (IPEG) in 2012. The survey was completed by 170 surgeons from 31 countries and only 60% of them routinely performed tracheoscopy before surgical repair of EA[4]. A lower rate of use (43%) was found by Zani *et al*[5] with a survey completed by 178 delegates from 45 countries who attended the European Pediatric Surgeons Association (EUPSA) and British Association of Pediatric Surgeons (BAPS) Joint Congress in Rome in 2012[5]. The Italian retrospective and prospective national register of EA compared the data of the 53 participating centers and the use of TBS stood at 40.5% (Pini Prato, personal communication 2013), while only 21.5% of the 38 centers of the French National Register performed TBS[3]. None of these studies mentioned which type of tracheoscope, rigid or flexible, was used, nor technical details of the procedure. In a British and Irish prospective cohort study on 151 children affected by EA, no data were reported in regards to the use of tracheoscopy[6]. Evidence suggests that TBS is still far from being a common practice in many international pediatric surgery centers. Possible explanations are the lack in many settings of adequate expertise in neonatal airways endoscopy and the availability of alternative diagnostic tools.

THE IMPORTANCE OF TBS

Overview on EA

Preoperative TBS has proven to be an useful diagnostic tool in newborns with EA[7,8]. This procedure helps to define the anatomy of the respiratory tree, confirms the presence of a proximal and/or distal tracheoesophageal fistula (TEF), the site of entry and location. The value of routine TBS is much debated because the incidence of the combination of a proximal and distal fistula has been historically reported in less than 1% of cases. Nevertheless, there is increasing evidence of a higher prevalence of double TEF[8]. Two studies also reported that the routine use of TBS led to detection of a much higher relative incidence of proximal fistula, up to 5.69%. This finding suggests that the lower rate of EA with proximal TEF reported in the literature when TBS is not performed is probably due to a lack of accuracy in the diagnosis[8,9]. The distance from the entrance of the distal fistula to the carina provides a clue as to the gap between the esophageal pouches as the location of the upper one could be suspected by observing an external compression of the pars membranacea. Water-soluble contrast inflated in a Fogarty catheter balloon positioned into the fistula at its entrance into the trachea provides a better assessment of the distance between the fistula and upper esophageal pouch and allows easier identification during surgery of a distal esophageal pouch. TBS also allows preoperative detection of unusual variants of AE, such as double or triple TEF fistula[10], and if gross changes or deviation of the vascularization of the subepithelium are found, the suspicion of an hidden TEF should be raised.

Diagnosis of associated anomalies

Associated tracheobronchial anomalies are present in nearly half of newborns with EA[9,11], including ectopic right upper bronchus, laryngotracheoesophageal cleft, tracheal stenosis, tracheobronchial vascular compression and laryngomalacia. The presence of an otorhinolaryngologist with expertise in neonatal settings is strongly recommended during the procedure in order to ensure early detection of associated anomalies of the respiratory tree as they can result in a significant perioperative and postoperative morbidity, such as difficulty in ventilation, failed extubation and atelectasis if their presence is unexpected[12]. Congenital vocal fold paresis/paralysis in particular, although uncommon, should be ruled out prior to surgical repair as it could lead to multiple failures in extubation[13]. Kosloke *et al*[14] reported that preoperative endoscopic findings influenced the operative technique or management in 24 of 42 newborns (57%), as in the case of an unexpected cervical TEF fistula which was repaired through a cervical approach without thoracotomy[14]. Bronchotracheomalacia can be clinically significant in 10% to 20% of children with EA, although it has been reported to be present in postmortem pathological specimens in nearly 75% of patients with EA[15]. A definitive diagnosis of tracheomalacia can be made by TBS with the child spontaneously breathing by detecting the typical triad of anteroposterior narrowing of the tracheal lumen, weakening of the semicircular-shaped cartilages and forward ballooning of the widened posterior membranous tracheal wall[1]. Limited to dynamic evaluation of the

Table 1 Review of the use of tracheobronchoscopy

Ref.	Type of study	Use of TBS (prevalence)	Setting
Lal *et al*[4]	Survey	60%	International Pediatric Endosurgery Group, Online-based Survey, 170 Pediatric Surgeons, 2012
Zani *et al*[5]	Survey	43%	European Pediatric Surgeons Association and British Association of Pediatric Surgeons Survey, 178 Pediatric Surgeons, 2012
Sfeir *et al*[3]	Prospective register	21.50%	French Reference Center for EA, 38 centers, 307 patients, 2008-2009
Burge *et al*[6]	Prospective cohort	-	Prospective Multicentric Cohort study, 151 patients, 2008-2009
Pini Prato (personal communication)	Prospective and Retrospective register	40.50%	Italian Group of Study on EA, 53 centers, 150 patients, 2011-2012

TBS: Tracheobronchoscopy; EA: Esophageal atresia.

airways, the flexible scope provides the best assessment for conditions such as epiglottic collapse, laryngomalacia, vocal cord paralysis, tracheabronchomalacia[16,17]. Nevertheless, Dodge-Khatami *et al*[18] reported that in 17 of the 20 newborns with an AE who developed a clinically-evident tracheomalacia, the pre-operative bronchoscopy was negative. Furthermore, according to Kosloske *et al*[14], TBS can accurately predict the position of the aortic arch by observing the side of dominant pulsation and it could change the side of the thoracotomy.

Complications

The duration of the procedure is short and the oxygen desaturation could be corrected by a facemask. Complications of both flexible and rigid bronchoscopy are related to anesthesia, ventilation and equipment use, generally occurring in less than 5% of cases. Minor complications include epistaxis, airway bleeding, cough and transient laryngospasm. Major complications include apnea, bradycardia and important oxygen desaturation with bronchospasm[16]. Spread of infections and mortality are extremely rare[16]. Flexible bronchoscopes are associated with problems of mechanical ventilation, which often poses a time limit of 30-45 s on this procedure[19,20]. Should ventilation become difficult, the tracheoscope may be removed and the ventilation can continue through the endoscope sheath. Ianolli *et al*[21] reported a case of pneumothorax during flexible TBS in a neonate with EA. Deanovic *et al*[22] reported two cases of accidental extubations during intermittent positive pressure ventilation (IPPV) and fiber optic tracheoscopy assisted repair of TEF (TARTEF) in 47 newborns, in whom the tracheoscope passed through the lumen of the tracheal tube and facilitated the identification of the TEF during surgery.

Contraindications and limits

No absolute contraindications to TBS are reported in newborns. Relative contraindications include pulmonary hypertension and uncorrected bleeding diathesis[16] but these conditions are quite uncommon in newborns with EA. Special attention should be paid to extremely low birth weight (ELBW) premature neonates as the narrow larynx and trachea do not allow the introduction of the even ultra slim 1.9 or 2.2 mm diameter flexible fiberscope without working channel. It is assumed that there must be at least a 2 mm difference between the size of the endoscope and the diameter of the larynx[16].

ALTERNATIVE DIAGNOSTIC TOOLS

Prone esophagogram

The need for contrast prone esophagogram is actually debated[9,19]. Under carefully controlled fluorography, water-soluble contrast can visualize the position of the dilated upper esophageal pouch and may detect a proximal TEF. However, this procedure requires a high degree of pediatric radiology expertise, involves radiation hazards and may be associated with complications, including aspiration pneumonia[8,19]. Mortality during a contrast study in newborns is extremely rare but reported[23]. Moreover, the esophagogram could give false negative results when the fistula is occluded by mucus or false positive results when the contrast identifies the tracheobronchial tree which is more likely to be aspiration through the larynx rather than through a proximal TEF[8,23]. We previously reported a statistically significant better accuracy in the diagnosis of proximal TEF using TBS rather than an esophagogram[8].

Ultrasound scan

Mediastinal sonography has been proposed to delineate the tracheoesophageal anatomy with promising results. Su *et al*[24] demonstrated no statistically significant difference in the distance between the two esophageal pouches as assessed by ultrasound scan (US) and surgery in 36 newborns. In a study performed by Gassner *et al*[25], a small volume of saline solution was instilled into the blind upper esophageal pouch and an ultrasound scan was performed. The examination detected two proximal fistulas in 16 patients and the fistula was located sonographically by detecting moving air bubbles in two newborns with isolated TEF[25]. Ultrasound scan with Doppler evaluation also identified the position of the aortic arch as well as associated malformations[25]. Increasing evidence suggests that an ultrasound scan is a useful noninvasive tool for the diagnostic assessment of newborns with EA and plays a crucial role in planning the surgical strategy. Nevertheless, this procedure is operator dependent and needs to be validated on a larger series of patients[9].

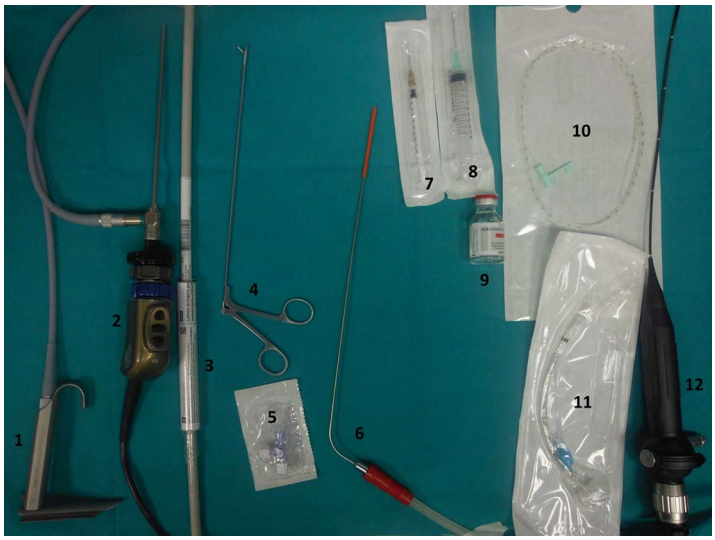

Figure 1 Tracheobronchoscopy instrumentation. 1: Open-sided laryngoscope with proximal prismatic lighting; 2: 2.7 mm neonatal rigid bronchoscope; 3: Fogarty catheter (size 3-4); 4: Bronchoscopy forceps; 5: Three-way stopcock; 6: Tracheoscope suction tube; 7: Insulin syringe (to inflate Fogarty catheter); 8: 10 mL syringe (to aspirate the contrast medium); 9: Water-soluble mean of contrast; 10: Nose gastric-tube 4-6 Fr; 11: Endotracheal tube; 12: Neonatal flexible fiberoptic bronchoscope.

Computed tomography

Computed tomography (CT) and three-dimensional imaging of the tracheobronchial system are well established in adults but experience with pediatric patients is limited. Su *et al*[26] found no differences in the distance between the two esophageal pouches as measured by CT scan and at surgery and the same results were achieved by Wen *et al*[27] by utilizing multidetector-row computed tomography (MDCT) in reconstruction of 3D volume rendering. Mahalik *et al*[28] found that in 20% of newborns with EA, the TEF fistula could not be recognized on a preoperative 3D CT scan, while Fitoz *et al*[29] reported that shaded surface display (SSD) and virtual bronchoscopy reconstruction techniques can satisfactorily show distal fistulae. A recent review of the 8 available studies on the topic suggests that the safety of CT scan techniques is questionable due to limited facilities, problems regarding neonatal transportation to the radiology department and the need for sedation. Moreover, although a modern CT gives low grade exposure, this examination is still associated with radiation hazards[30]. Mahalik showed a risk of 1.79 radiation induced cancer per 10000 newborns[28]. The routine use of preoperative CT scans in newborns with EA is controversial as the limited information acquired that may help to change the surgical plan can be easily obtained by TBS or intraoperatively.

Magnetic resonance imaging

The experience with MRI in newborns affected by EA is extremely limited[9]. Cantinotti *et al*[31] consider this method to be an important diagnostic tool in identifying anomalies of the aortic arch and associated cardiac anomalies. Nevertheless, the advantages of the visualization of tracheobronchial and esophageal system have not been studied yet and the need for general anesthesia makes magnetic resonance imaging (MRI) a procedure only for selected cases.

CONCLUSION

Routine preoperative TBS with a rigid tracheoscope has proven to be most useful in the diagnostic and therapeutic assessment of newborns affected by esophageal atresia as this procedure enables an anatomical definition of the anomaly better than other diagnostic tools. The presence of an otorhinolaryngologist with expertise in neonatal settings is strongly recommended during the procedure to allow early detection of associated anomalies of the respiratory tree which can result in a significant perioperative and postoperative morbidity if not detected. When the distal TEF is cannulated by a Fogarty catheter, TBS may facilitate the surgical repair and improve the mechanical ventilation. Although TBS is not a routinely part of the management in many international centers, increasing evidence suggests that this procedure should be strongly recommended in the management of neonates affected by esophageal atresia.

TBS should performed in the operation room just before surgical repair[7,8]. Instrumentation requested is illustrated in Figure 1. The presence of an otorhinolaryngologist with expertise in a neonatal setting is strongly recommended and close communication with the anesthesiological and surgical team is essential to perform a safe TBS[2]. Electrocardiography and peripheral oxygen saturation must be obtained. Particular attention should be paid to any abnormality of the neck or spine that might make the insertion of the endoscope difficult[11-32]. After inhalatory induction with halogenated ether (sevoflurane), the child is maintained in spontaneous ventilation and 100% oxygenation is achieved with a facemask. During laryngoscopy, a local anesthetic such as 0.5%-2% lidocaine should be applied to the vocal cords and larynx. Lidocaine may be instilled directly, sprayed or nebulized and the total dose should not exceed 5-7 mg/kg[16]. Insufficient topical anesthesia could result in pain, cough, laryngospasm or bronchospasm, usually due to vagal stimulation. We concur with the recommendation[11] of inserting a nasopharyngeal tube to provide oxygen and sevoflurane during the procedure. After visualization of the vocal cords, the neonate should be positioned with a small roll under the shoulders to slightly extend the neck and the tracheoscope should be pushed gently to enter

the trachea. The endoscope must be slowly brought down to the carina and then withdrawn more slowly to look for the presence of fistulas or other anomalies. A video recording system with magnification facilitates visualization of the tracheobronchial anatomy and allows an immediate collegial discussion of the findings. Higher quality images are provided by rigid scopes[33]. If no proximal TEF is recognized, 10 mL of air should be injected through a gastric tube positioned in the upper esophageal pouch as very small or occluded fistulas could be missed. Mechanical ventilation can be facilitated by the placement of a 3-4 Ch Fogarty catheter relative to the child's weight to occlude the distal tracheoesophageal fistula, thus avoiding gastric overdistension and gastroesophageal reflux[32]. Before the insertion of the Fogarty, we suggest placing a nasogastric tube through the mouth, parallel and external to the endoscope, which is advanced through the fistula into the stomach to aspirate gastric secretions. At this point, the balloon is inflated with 0.2-0.75 mL of water-soluble contrast under tracheoscopic control, retracted up to the entrance of the fistula in the trachea. This maneuver allows better assessment of the distance between the distal fistula and the tip of the endoscope or the radiopaque gastric tube subsequently positioned at the bottom of the upper esophageal pouch at chest X-ray. Furthermore, the inflated Fogarty balloon provides a gentle dilatation of the lower pouch, which makes easier the esophagoesophageal anastomosis. In patients with H-type TEF, Atzori *et al*[2] advocates cannulation of the fistula by the insertion of a guide wire through the trachea and withdrawn through the mouth under fluoroscopy[2,33]. With this procedure, the H-fistula can be localized and lifted upwards to enable a cervical approach and avoid thoracotomy[2]. TBS also allows a correct positioning of the endotracheal tube which should be placed above the carina but below any fistula present[11] at an appropriate depth which can be assessed by flexible tracheoscopy through an adaptor on the facemask.

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RETROSPECTIVE STUDY

Endoscopic band ligation for bleeding lesions in the small bowel

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Abstract

AIM: To investigate the safety and efficacy of endoscopic band ligation (EBL) for bleeding lesions in the small bowel.

METHODS: This is a retrospective study evaluating EBL in six consecutive patients (three males, three females, 46-86 years of age) treated between May 2009 and February 2014: duodenal vascular ectasia; 1, jejunal bleeding diverticulum; 1, ileal Dieulafoy's lesion; 1 and ileal bleeding diverticula; 3. The success of the initial hemostasis was evaluated, and patients were observed for early rebleeding (within 30 d after EBL), and complications such as perforation and abscess formation. Follow-up endoscopies were performed in four patients.

RESULTS: Initial hemostasis was successfully achieved with EBL in all six patients. Eversion was not sufficient in four diverticular lesions. Early rebleeding occurred three days after EBL in one ileal diverticulum, and a repeat endoscopy revealed dislodgement of the O-band and ulcer formation at the banded site. This rebleeding was managed conservatively. Late rebleeding occurred in this case (13 and 21 mo after initial EBL), and re-EBL was performed. Follow-up endoscopies revealed scar formation and the disappearance of vascular lesions at the banded site in the case with a duodenal bleeding lesion, and unresolved ileal diverticula in three cases. Surgery or transarterial embolization was not required without any complications during the median follow-up period of 45 (range, 2-83) mo.

CONCLUSION: EBL is a safe and effective endoscopic treatment for hemostasis of bleeding lesions in the small bowel.

Key words: Endoscopic band ligation; Small bowel; Diverticular hemorrhage; Jejunal bleeding; Ileal bleeding; Therapeutic endoscopy; Hemostasis

Core tip: There have been few reports regarding the use of endoscopic band ligation (EBL) for the treatment of bleeding lesions in the small intestine. The present study demonstrates safe and effective use of EBL to treat six patients with small bowel lesions including, duodenal vascular ectasia, ileal Dieulafoy's lesion, and jejunal and ileal bleeding diverticula. Although the bleeding was successfully managed in all patients, those with diverticular bleeding in the small bowel should be closely monitored after an initial EBL.

Ikeya T, Ishii N, Shimamura Y, Nakano K, Ego M, Nakamura K, Takagi K, Fukuda K, Fujita Y. Endoscopic band ligation for bleeding lesions in the small bowel. *World J Gastrointest Endosc* 2014; 6(10): 488-492 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i10/488.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i10.488

INTRODUCTION

Endoscopy can be used to both diagnose and treat bleeding in the small bowel. Enteroscopic techniques such as argon plasma coagulation (APC) and endoscopic clipping have been well studied[1-5]. Endoscopic band ligation (EBL) had been used for the treatment of esophageal varices[6-10]. Recently, EBL has been applied for hemostasis of colonic diverticular hemorrhage[11-15] and non-variceal upper gastrointestinal bleeding[16-20]. There are some reports concerning the use of EBL for treating small intestinal bleeding lesions[13,21-23], though the safety and efficacy of this use has not been established. However, a recent report indicates that EBL is unsafe and unsuitable for hemostasis in the small bowel[24,25]. Therefore, the aim of this study was to retrospectively investigate the safety and efficacy of EBL for the treatment of bleeding lesions in the small bowel.

MATERIALS AND METHODS

Patient population

For this study, six consecutive patients (three males and three females, between 46 and 86 years of age) that were admitted to St. Luke's International Hospital and treated with EBL for gastrointestinal bleeding between May 2009 and February 2014 were included. After receiving standard supportive medical care including fluid resuscitation and hemodynamic monitoring, endoscopy was performed for the diagnosis and treatment of the bleeding lesions in the small bowel, including a duodenal vascular ectasia (one case), jejunal bleeding diverticulum (one case), ileal Dieulafoy's lesion (one case) and ileal bleeding diverticula (three cases). A bleeding diverticulum was defined as a diverticulum with stigmata of recent hemorrhage such as active bleeding, a non-bleeding visible vessel, or an adherent clot[26,27]. Informed written consent was obtained from all patients for endoscopy and EBL.

Endoscopic procedures

For the duodenal vascular lesion, a colonoscopy (PCF-Q260JI; Olympus Medical Systems, Tokyo, Japan) rather than a gastroscopy was performed because the lesion was located at the horizontal portion of the duodenum. To treat the jejunal bleeding diverticulum, double-balloon enteroscopy (EN-450P5/20; Fujifilm Co., Tokyo, Japan) was performed. Colonoscopies were performed for the four ileal lesions following bowel preparation with polyethylene glycol. Bleeding lesions were identified and marked with hemoclips or by injecting carbon ink near the lesions. The endoscope was then reinserted after a band-ligator device (MD-48710 EVL Devices; Sumitomo Bakelite Co Ltd., Tokyo, Japan) was attached to the tip. The lesions were suctioned into the ligator cup, and the O-band was released. A repeat endoscopy was performed in the event of rebleeding after EBL. The success of the initial hemostasis, the incidence of early rebleeding (within 30 d after EBL), and complications such as perforation and abscess formation were evaluated retrospectively. Eversion after EBL was assessed in the diverticular lesions[12,15]. Follow-up endoscopies were performed.

RESULTS

The characteristics of the six cases of bleeding lesions and results from the EBL are presented in Table 1. EBL was completed, and initial hemostasis was achieved in all the patients. Endoscopic views of the duodenal vascular ectasia and EBL procedure are shown in Figure 1. Eversion was not sufficient after EBL in the diverticular lesions (Figure 2A-C). Early rebleeding occurred in one case of ileal diverticulum (case 5) 3 d after EBL. A repeat endoscopy in this case revealed dislodgement of the O-band and ulcer formation at the banded site (Figure 2D). It was managed conservatively, and additional treatments such as endoscopic hemostasis or surgery were not required. A six-month follow-up endoscopy for the duodenal case revealed scar formation and the disappearance of vascular lesions at the banded site. However, EBL was unable to resolve three of the ileal diverticula as observed during follow-up endoscopies performed 3 to 29 mo after the initial EBL (cases 4, 5 and 6). Follow-up endoscopies were not performed for the jejunal diverticular (case 2) and ileal Dieulafoy's (case 3) lesions. Late rebleeding occurred in the ileal case (case 5; 13 and 21 mo after initial EBL), and re-EBL was performed. Surgery or transarterial embolization was not required, and no complications were reported in any of the cases during the median follow-up period of 45 (range, 2-83) mo.

DISCUSSION

This is a retrospective case series demonstrating the use of EBL for the treatment of bleeding lesions in the small bowel. For these procedures, a band-ligator device commonly available for the treatment of esophageal varices was used, which has recently been used for colonic diverticular hemorrhage[11-15]. EBL was successful in achieving immediate hemostasis in all cases, despite the limited operability of the endoscope within the reduced diameter of the small bowel relative to other digestive tracts. In addition, hemostatic methods are also restricted by the thin walls of the small bowel, which are vulnerable to perforation during contact coagulation. However, no such complications occurred in the present study. EBL is not hindered by difficult positioning of bleeding lesions or endoscope instability because it is not necessary to place the lesions in the same direction of the endoscopic working channel.

Although eversion of colonic bleeding diverticula can be obtained with EBL[11-15], it was not observed in the diverticular lesions of the small bowel. Insufficient eversion may be the cause for the early dislodgement of the O-band and early rebleeding that occurred in one case of an ileal diverticulum, though it was managed conservatively without the need for additional treatments. How-

Table 1 Characteristics and results of small bowel bleeding lesions treated with endoscopic band ligation

Case	Age	Sex	Bleeding lesion	Location	EBL successful	Eversion after EBL	Procedural time (min)	Complications	Early rebleeding
1	86	F	Vascular ectasia	Duodenum	Yes	Yes	31	None	No
2	62	M	Diverticular bleeding (non-bleeding visible vessel)	Jejunum	Yes	No	168	None	No
3	61	F	Dieulafoy's lesion	Terminal ileum	Yes	Yes	38	None	No
4	46	M	Diverticular bleeding (active bleeding)	Terminal ileum	Yes	No	58	None	No
5	85	F	Diverticular bleeding (adherent clot)	Terminal ileum	Yes	No	80	None	Yes
6	71	M	Diverticular bleeding (adherent clot)	Terminal ileum	Yes	No	58	None	No

EBL: Endoscopic band ligation.

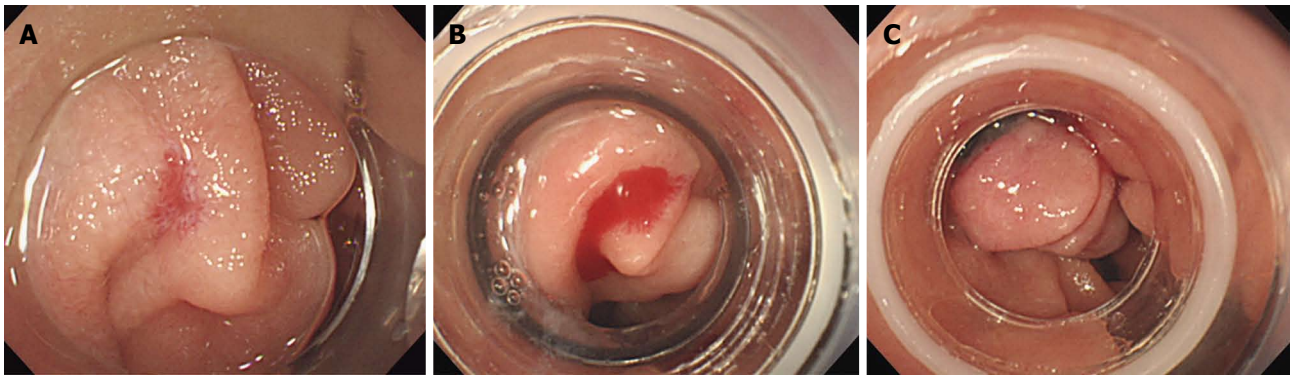

Figure 1 Endoscopic views of the vascular ectasia. A: Bleeding at the horizontal portion of the duodenum; B: View through the band-ligator device; C: Endoscopic band ligation was performed.

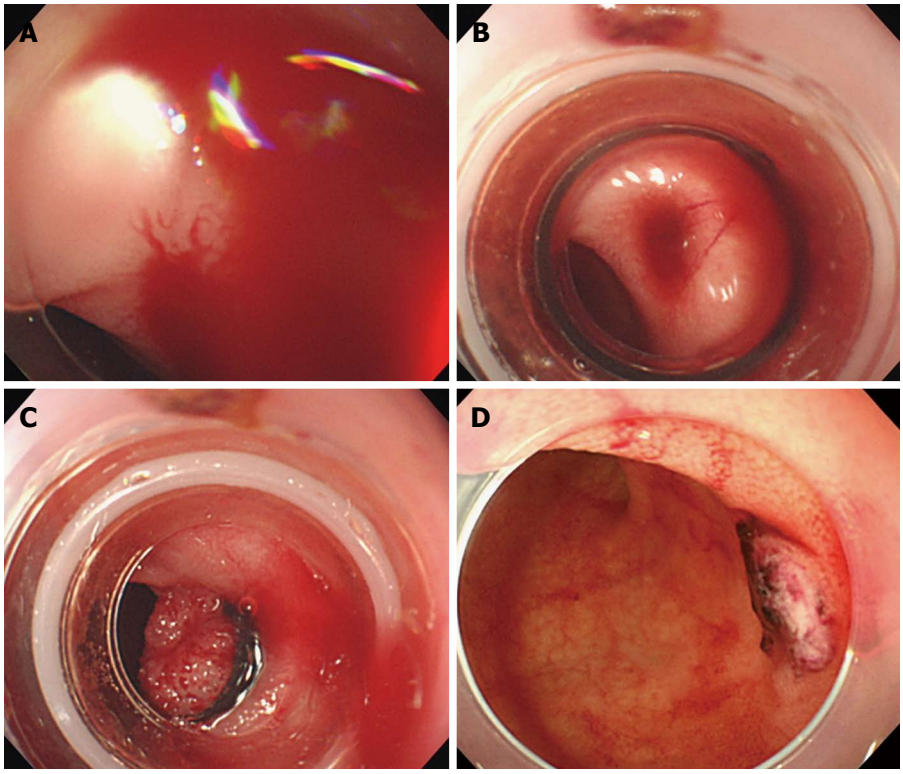

Figure 2 Endoscopic views of the ileal diverticulum. A: Active bleeding; B: View through the band-ligator device; C: Endoscopic band ligation was performed. However, eversion of the banded diverticulum was not sufficient; D: Repeat endoscopic view of O-band dislodgement and ulcer formation at the banded site.

ever, late rebleeding from the same diverticula might not be prevented, as EBL did not resolve bleeding diverticula in the small bowel.

The length of the EBL procedure is an important issue, though it was not compared with alternatives in the present study. For this procedure, the endoscope must be withdrawn in order to attach the band-ligator device, and then reinserted. In the current study, procedural time was minimized by marking the identified bleeding lesions with hemoclips or carbon ink, which could be easily detected during the re-insertion of the endoscope. In addition, this study demonstrated the safety of the EBL procedure. It was reported that EBL was not safe for treatment of the small bowel, as histologic evaluation revealed inclusion of the muscularis propria and serosa by the band-ligator[24,25]. There were no complications or instances of perforation or penetration in the present study, though the study was limited to only six cases.

In conclusion, although it might be precarious to draw conclusions from small sample size and more data was needed to evaluate the use of EBL in small intestine lesions, the results of the present study indicate that EBL may be a safe and effective endoscopic treatment for bleeding lesions in the small bowel. However, patients with diverticular bleeding in the small bowel should be closely monitored after initial EBL. Further studies incorporating larger patient populations will help to validate the safety and efficacy of this procedure.

COMMENTS

Background

Single-balloon, double-balloon, and capsule endoscopies are commonly and widely used treatment procedures. Endoscopic band ligation (EBL) is a procedure that has been used to treat colonic diverticular hemorrhage, though it has not been thoroughly evaluated as a viable treatment option for small intestinal bleeding, despite its increasing incidence.

Research frontiers

EBL is considered to be a useful and safe treatment for esophageal varices and colonic diverticular hemorrhaging. Although the safety and efficacy of EBL for treatment of small intestinal bleeding is not known, a recent report indicates that it can result in inclusion of the muscularis propria and serosa of the small bowel.

Innovations and breakthroughs

This study is the first to report on the use of EBL for treatment of patients with duodenal, jejunal, and ileal bleeding. In all six cases, immediate hemostasis was achieved with no complications, such as perforation or abscess formation.

Applications

The results of this study suggest that EBL is a safe and effective option to achieve hemostasis in the small bowel.

Terminology

Endoscopic band ligation is an endoscopic technique involving elastic bands to treat varices. Diverticular hemorrhaging of the small intestine can involve the duodenum, jejunum or terminal ileum. Dieulafoy's lesion is a lesion with a dilated tortuous arteriole. Vascular ectasia is dilated small blood vessel.

Peer review

The manuscript titled as "Endoscopic band ligation for bleeding lesions in the small bowel" is a large patient series which describes the method of treatment of bleeding originated from small bowel. Tt can be published due to its originality.

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RETROSPECTIVE STUDY

What can be the criteria of outpatient-based endoscopic resection for colon polyp?

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Abstract

AIM: To investigate whether out-patient based endoscopic mucosal resection (EMR) for colon polyps ⩽ 10 mm is safe.

METHODS: Between January 2004 and December 2012, a total of 3015 EMR cases conducted in 1320 patients were retrospectively reviewed. The factors contributing delayed hemorrhage were analyzed. We calculated the probability of delayed bleeding after stratifying conditions of specific risk factors.

RESULTS: The size of the polyp (95%CI: 1.096-1.164, $P < 0.001$) and patients with chronic renal failure (95%CI: 1.856-45.106, $P = 0.007$) were identified as independent risk factors for delayed bleeding in multivariate analysis. 95%CI for percent of delayed bleeding according to polyp size was determined for the following conditions: size ⩽ 10 mm, 0.05%-0.43%; 20 mm ⩾ size > 10 mm, 0.54%-2.08%; size > 20 mm, 4.22%-11.41%. 95%CI was determined for the risk of serious immediate bleeding for a polyp ⩽ 10 mm was 0.10%-0.56%. Finally, 95%CI for percent of incomplete resection was 0.07%-0.49% in polyps ⩽ 10 mm.

CONCLUSION: It seems acceptable to perform outpatient-based EMR for colon polyps ⩽ 10 mm.

Key words: Colon; Polyp; Endoscopic mucosal resection; Bleeding

Core tip: There has been a belief that it is safe to perform outpatient-based endoscopic mucosal resection (EMR) for a colon polyp ⩽ 10 mm. We found out that the risk of delayed bleeding was 0.05% to 0.43% and that the risk of serious immediate bleeding was 0.10% to 0.56% in polyps ⩽ 10 mm. From these results, we induced the conclusion that outpatient-based EMR for polyps no more than 10 mm can be performed without serious concern.

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INTRODUCTION

Endoscopic mucosal resection (EMR), by snare polypectomy for a pedunculated type or by injection and cutting for a sessile type, is the most common method for removing colon polyps[1] and is widely performed in

many clinical fields, from small private clinics to tertiary hospitals. EMR technique should be focused on efficient removal and minimal complication[2]. The most frequent complication is bleeding[3]. Bleeding can be categorized as either immediate or delayed depending on the onset time. Immediate bleeding just after the procedure can be easily managed with recent advancing endoscopic technology and hemostasis equipment[4-6], but delayed hemorrhages causes more serious problem because of unpredictable onset and occurrence after hospital discharge[3,7]. Several research studies showed that locations and the types of polyp could be risk factors for delayed bleeding[4,7,8]. However, the size of the polyp was determined to be the most reliable factor for delayed bleeding[8-11]. Although many endoscopists believe that it is safe to perform outpatient-based EMR for a polyp no more than 10 mm, no definite report about the possibility of delayed bleeding associated with specific conditions of alleged risk factors has been published. In this study, we calculated the possibility of delayed bleeding according to specific situations of risk factors to understand conditions in which outpatient-based EMR can be performed.

MATERIALS AND METHODS

Patients

We retrospectively reviewed all of the patients that underwent an EMR for a colon polyp between January 2004 and January 2013 at the Gospel Hospital, Kosin University College of Medicine. The institutional review board approved the study protocol. Patients with submucosal tumors, hereditary polyposis syndrome, and inflammatory bowel disease such as Crohn's disease and ulcerative colitis, were excluded. Endoscopic submucosal dissection cases were also excluded because we wanted to focus on understanding the safety and efficacy of EMR.

Definition

Two conditions were used to define delayed bleeding in the outpatient setting. The first condition was when the patient experienced more than one episode of hematochezia at least one hour after EMR. The second condition was identifiable evidence of hemorrhage from an EMR site; this was established to differentiate delayed bleeding from blood passing during EMR. Immediate serious bleeding was defined as bleeding which required hemostatic clipping (Easy clips; Olympus Ltd., Tokyo, Japan) just after EMR. Histological complete resection was defined when there was no tumor involvement at horizontal and vertical margins. A complete endoscopic resection was defined when en bloc resection was achieved.

Colonoscopy preparation and endoscopic mucosal resection

Patients were instructed to discontinue the use of anticoagulant or anti-platelet therapy at least 5 to 7 d before endoscopic procedures. The patient's blood count and coagulation laboratory were measured. Patients were recommended to have a 72 h-fiber-free diet and an 8 h-4-L polyethylene glycol solution to prepare colonoscopy. 25-50 mg of meperidine (Demerol®) was administered intravenously for reducing pain during the colonoscopy. Conscious sedation colonoscopy was performed with 0.05-0.07 mg/kg of initial midazolam, an additional 1-3 mg of midazolam was injected at the discretion of the practitioner if the patient expressed pain.

Endoscopic mucosal resection and observation

The procedure was performed with electronic video colonoscopes (types Q260AL and H260AI; Olympus, Tokyo, Japan). Electrosurgery was performed using ICC 200 (ErbeElektromedizin GmbH, Tübingen, Germany) or a VIO 300D APC2 (ErbeElektromedizin GmbH, Tübingen, Germany). Fours killed endoscopists, each with at least 5 year-experiences with EMR, performed the procedures. Snare polypectomy without submucosal injection was performed for pedunculated polyps. Open snare was placed around the stalk of a pedunculated polyp and was gently grasped. After snare excision, the colon was expanded again to visualize the resection area. For sessile polyps, submucosal injections were performed. The injection solution was composed of saline and epinephrine (1:100000). Injection volume usually ranged from 5 cc to 30 cc. Close observation was applied to each lesion during and after submucosal injection for excluding the presence of a non-lifting sign. EMR was canceled if there was a non-lifting sign. After then, a biopsy was performed and the patient was transferred to surgical unit. *En bloc* EMR was regarded as complete endoscopic resection of a lesion, and piecemeal EMR was defined when multiple snaring was used. Hot biopsy forceps (FD-1U-1 or FD-1U-2, Olympus Ltd., Tokyo, Japan) were applied to ablate the possible bleeding foci in EMR-related ulcers. If there was serious immediate bleeding, hemostatic clips were applied to control the bleeding and prevent possible delayed bleeding. After EMR, all patients were hospitalized for at least 18 h, and they revisited the outpatient clinic 7 to 14 d after discharge for histologic assessment and to report delayed bleeding or other discomfort.

Histopathologic evaluation

All resected tissue was collected by a basket or through the suction channel. The size of each polyp was measured. Vienna criteria was applied for histological diagnosis of colorectal neoplasms[12]. Reconstruction of separated specimens was performed to evaluate the horizontal and vertical margins. All resected specimens were evaluated histologically at low-power and high-power magnification using light microscopy.

Urgent colonoscopy and bleeding control

Reported cases of hematochezia after EMR were confirmed by an attending physician by assessing blood on a digital rectal examination. To check the lesions and

Table 1 Baseline characteristics of patients with colon polyps removed by endoscopic mucosal resection *n* (%)

	n = 3015
Age, mean ± SD, yr	59.6 ± 10.4
Male	1771 (70.0)
Comorbidity	
Hypertension	564 (18.7)
Cardiovascular or cerebrovascular disease	389 (12.9)
Chronic renal failure	23 (0.8)
Liver cirrhosis	75 (2.5)
Diabetes mellitus	157 (5.2)
Cancer history	353 (11.7)
Anti-coagulants and anti-platelets	
Aspirin	253 (8.3)
Clopidogrel	57 (1.9)
Warfarin	43 (1.4)
Size of lesion, mean ± SD, mm	11.1 ± 6.8
Locations	
Right side colon	1296 (43.0)
Cecum	109 (3.6)
Ascending colon	805 (26.7)
Transverse colon	382 (12.7)
Left side colon	1719 (57.0)
Descending colon	346 (11.5)
Sigmoid colon	817 (25.9)
Rectum	556 (18.4)
Morphologic classification	
Pedunculated type	550 (18.2)
Piecemeal resection	130 (4.3)
Pathologic complete resection	2956 (98.0)
Horizontal margin involvement	31 (1.0)
Vertical margin involvement	10 (0.3)
Serious immediate bleeding[1]	78 (2.6)
Prophylactic hemostatic clipping	345 (11.4)
Delayed bleeding	25 (0.8)
Spurting, *n*	2
Oozing, *n*	13
Clots with or without vessel exposure, *n*	10
Onset of delayed post-EMR bleeding, mean ± SD (range), h	9.9 ± 0.4 (7-72)
Perforation	6 (0.2)
Histology	
Adenoma	2357 (78.2)
Tubular adenoma	2026 (67.2)
Tubulovillous adenoma	233 (7.7)
Villous adenoma	99 (3.3)
Serrated adenoma	66 (2.2)
Carcinoma	89 (3.0)
Submucosal invasive carcinoma	10 (0.3)
Hyperplastic polyp	413 (13.6)
Others	90 (3.0)

[1]Serious immediate bleeding was defined as bleeding which required hemostatic clip application just after EMR. EMR: Endoscopic mucosal resection.

to stop bleeding, an emergent colonoscopy was always performed. When an EMR site of delayed bleeding was identified, hemostasis was performed immediately. Clipping was done to control large bleeding or non-bleeding vessels, and hot biopsy forceps was performed for coagulating small vessels or locations where placing hemostatic clips was difficult due to tissue consolidation.

Variables

The risk factors for delayed bleeding were analyzed in the view of the patients' condition, polyp characteristics, and the procedure. Patient-related factors included age, sex, comorbidities, and the use of antiplatelet agents or anticoagulants. The factors related with the characteristics of polyp such as size, location, shape, and pathologic result were investigated. The size of the polyp was measured and compared with the size of the biopsy forceps. The polyp shapes were categorized as sessile or pedunculated. The polyp locations within cecum, ascending colon, and transverse colon were classified as right colon, and the others were regarded as left colon. Based on pathologic reports, the polyps were differentiated as adenocarcinoma, adenoma, or others. Laboratory evaluation before EMR included platelet count, prothrombin time, and activated partial thromboplastin time. Procedure-related factors included *en bloc vs* piecemeal resection and the presence of serious, immediate bleeding followed by hemostatic clipping.

Statistical analysis

Statistical analysis was performed using the Statistical Analysis System software for Windows (version 9.2; SAS Institute, Cary, NC, United States). Depending on the presence of delayed bleeding, the patient characteristic distributions were analyzed using *T*-test or Mann-Whitney *U* test for continuous variables, whereas the χ^2 test or Fisher's exact test were used to analyze categorical variables. Statistical significance was set at $P < 0.05$, and if there was more than one predictor with a significant difference by univariate analysis, multivariate analysis using a logistic regression model was planned. Furthermore, we planned to calculate 95%CI or proportion to understand the possible risk of specific factors in conditioned situations.

RESULTS

General characteristics

Data were investigated for 3015 polyps, from 1320 patients who were treated by EMR during a 9-year period. The clinical data and demographics of patients and colon polyp characteristics are presented in Table 1. The mean (± SD) age of the patients was 59.6 ± 10.4 years. The mean (± SD) polyp size was 11.1 ± 6.8 mm, and the most common location was the sigmoid colon, which was identified in 817 cases (25.9%). The pedunculated type occurred in 18.2% (550 cases), and 3.0% (89 cases) of investigated polyps were carcinomas. Ten cases showed submucosal invasion. Piecemeal resection was performed for 130 cases (4.3%). There was serious bleeding which required clipping just after EMR in 78 cases (2.6%). Delayed bleeding occurred in 25 cases (0.8%). The mean onset of delayed bleeding was 9.9 ± 0.4 h. Perforation was observed in six cases (0.2%), and all cases were successfully managed by clips. Prophylactic hemostatic clipping was done for 345 (11.4%) EMR sites in order to prevent possible delayed bleeding.

Delayed bleeding group and uneventful group comparisons

There were no differences between the delayed bleeding and uneventful groups in age, sex, and pre-EMR labora-

Table 2 Comparison between the delayed bleeding group and the uneventful group *n* (%)

	Delayed bleeding *n* = 25	Uneventful group *n* = 2990	*P* value
Age, mean ± SD, yr	58.4 ± 10.1	59.6 ± 10.4	0.646
Male	15 (60.0)	1756 (58.7)	0.898
Laboratory before EMR			
Hemoglobin, g/dL	13.2 ± 1.4	13.66 ± 1.8	0.187
Platelet, × 10^3 count/mm^3	60.5 ± 12.1	71.9 ± 1.3	0.81
Prothrombin time, INR	0.984 ± 0.067	0.989 ± 0.528	0.785
Activated partial thromboplastin time, s	33.8 ± 4.4	34.9 ± 23.2	0.665
Comorbidity			
Hypertension	5 (20.0)	559 (18.7)	0.800
Cardiovascular or cerebrovascular disease	5 (20.0)	384 (12.8)	0.362
Chronic renal failure	2 (8.0)	21 (0.7)	0.015
Liver cirrhosis	1 (4.0)	74 (2.5)	0.131
Diabetes mellitus	3 (12.0)	154 (5.1)	0.140
Cancer history	3 (12.0)	350 (11.7)	1.000
Anti-coagulants and anti-platelets			
Aspirin	3 (12.0)	250 (8.4)	1.000
Clopidogre[1]	1 (4.0)	56 (1.9)	0.381
Warfarin	0 (0.0)	43 (1.4)	1.000
Size of lesion, mean ± SD, mm	25.8 ± 11.6	11.0 ± 6.6	< 0.001
Locations			
Right side colon[1]	8 (32.0)	1288 (43.1)	0.314
Morphologic classification			
Pedunculated	11 (44.0)	539 (18.0)	0.003
Piecemeal resection	6 (24.0)	124 (4.1)	0.001
Pathologic complete resection	25 (100.0)	2954 (79.9)	1.000
Horizontal margin involvement	0 (0.0)	31 (1.0)	1.000
Vertical margin involvement	0 (0.0)	10 (0.3)	1.000
Serious immediate bleeding[2]	3 (12.0)	75 (2.5)	0.025
Prophylactic hemostatic clipping	4 (16.0)	341 (11.4)	0.319
Histology			
Adenoma	23 (92.0)	2337 (78.2)	0.140
Carcinoma	1 (4.0)	88 (18.4)	0.529
Hyperplastic polyp	1 (4.0)	412 (13.8)	0.240
Others	0 (0.0)	90 (3.0)	1.000

[1]Right side colon includes cecum, ascending colon and transverse colon; [2]Serious immediate bleeding was defined as bleeding which required hemostatic clip application after EMR. EMR: Endoscopic mucosal resection.

tory results. The size of the polyp was much greater in the delayed bleeding group (25.8 ± 11.6 *vs* 11.0 ± 6.6; $P < 0.001$). The pedunculated-type polyp was more frequently observed in the delayed bleeding group ($P = 0.003$). Piecemeal resection and serious immediate bleeding were more frequently noticed in the delayed bleeding group ($P = 0.001$ and $P = 0.025$). Patients with chronic renal failure showed significant correlation with delayed bleeding ($P = 0.015$). There were no significant differences in the locations or histologic types of the polyps. A comparison of the delayed bleeding group and the uneventful group are presented in Table 2.

Independent risk factors for delayed bleeding

Logistic regression used for multivariate analysis revealed that size [Odds ratio (OR) = 1.129, 95%CI: 1.096-1.164, $P < 0.001$] was an independent risk factor for delayed bleeding (Table 3). Furthermore, chronic renal failure was revealed to independently increase the delayed bleeding (OR = 9.150, 95%CI: 1.856-45.106, $P = 0.007$).

Table 3 Multivariate analysis to define independent risk factors for delayed bleeding

	OR	95%CI	*P* value
Size	1.129[1]	1.096-1.164	< 0.001
Pedunculated type	1.497	0.634-3.534	0.357
Immediate serious bleeding	9.150	0.591-3.506	0.413
Piecemeal resection	2.265	0.815-6.292	0.117
Chronic renal failure	9.150	1.856-45.106	0.007
Immediate post-EMR bleeding[2]	1.447	0.597-3.506	0.413

[1]The risk of delayed bleeding after endoscopic mucosal resection increases 12.9% as the size of the polyp increases 1 mm; [2]Serious immediate bleeding was defined as bleeding which required hemostatic clip application.

The risk of delayed bleeding according to polyp size

95%CI for percent of delayed bleeding in this study was 0.05% to 0.43% (3/2061) in polyps that were no more than 10 mm in size (Figure 1). 95%CI for percent of delayed bleeding was between 0.54% and 2.08% (8/754) as the polyp size was more than 10 mm and no more than 20 mm. In the situation that the polyp size was more than 20 mm, 95%CI for percent of delayed bleeding increased dramatically, 4.22%-11.41% (14/200).

The risk of serious immediate bleeding according to polyp size

95%CI for percent of serious immediate bleeding in this study was 0.10% to 0.56% (5/2061) in polyps that were no more than 10 mm in size (Figure 2). 95%CI for percent of serious immediate bleeding was between 2.80% to 5.62% (30/754). The condition that the polyp size was over 10 mm and no more than 20 mm. As the polyp size was more than 20 mm, 95%CI for percent of serious immediate bleeding increased enormously, 16.37%-27.70% (43/200).

Incomplete resection according to polyp size

95%CI for percent of incomplete resection was 0.07% to 0.49% (4/2061) when the polyp size was no more than 10 mm (Figure 3). As the size of polyp increased, the 95%CI for percent of incomplete resection increased exponentially: 20 mm ⩾ Size > 10 mm 0.82%-2.59% (11/754) and Size > 20 mm, 6.97%-15.52% (21/200).

DISCUSSION

Our study confirmed that polyp size is the substantial risk factor for delayed bleeding which was discussed in previous reports[8-11]. The risk increased by 12.9% (95%CI: 1.096-1.164) per mm increase in diameter; this result was similar to previous investigations[10,11]. The type of polyp, whether sessile or pedunculated, was not a risk factor for delayed bleeding in the present study like other literature[7,9,13,14]. Histologic findings and location did not influence the occurrence of delayed bleeding either.

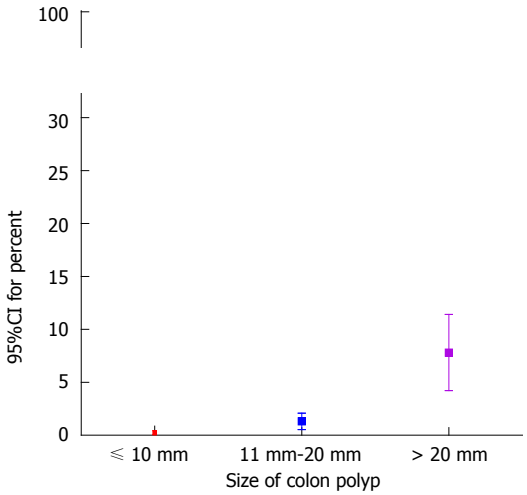

Figure 1 95%CI for percent of delayed bleeding risk according to polyp size: size ≤ 10 mm, 95%CI for percent = 0.05%-0.43%; 20 mm ≥ size > 10 mm, 95%CI for percent: 0.54%-2.08%; size > 20 mm, 95%CI for percent: 4.22%-11.41%.

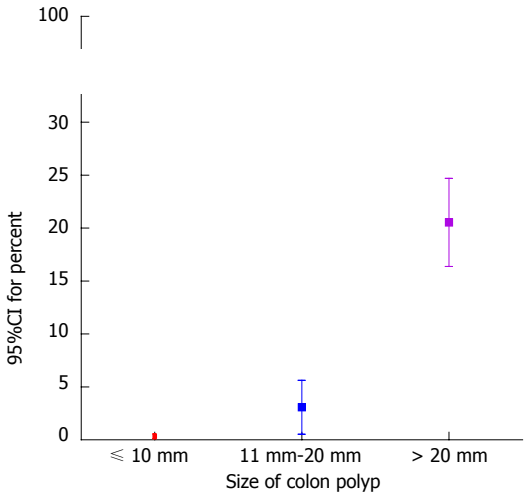

Figure 2 95%CI for percent of serious immediate bleeding risk according to polyp size: size ≤ 10 mm, 95%CI: 0.10%-0.56%; 20 mm ≥ size > 10 mm, 95%CI: 2.80%-5.62%; size > 20 mm, 95%CI: 16.37%-27.70%.

We calculated the risk of delayed bleeding according to the polyp size because we needed to determine the size of polyps that can be removed by outpatient-based EMR. The risk of delayed bleeding was 0.05% to 0.43% when the polyp size was no more than 10 mm. Serious immediate bleeding causes the procedure to be unstable and can require a patient hospitalized for close observation. In our investigation, serious immediate bleeding occurred in 2.6% (78/3015) of all cases, and this frequency was in the range of a previous report, 1.5% to 2.8%[15]. The risk of serious immediate bleeding was 0.10% to 0.56% in polyps ≤ 10 mm. In our perspective, the risk of delayed bleeding and the risk of immediate bleeding were so low that we were able to conclude outpatient-based EMR for polyps no more than 10 mm can be performed without serious concern.

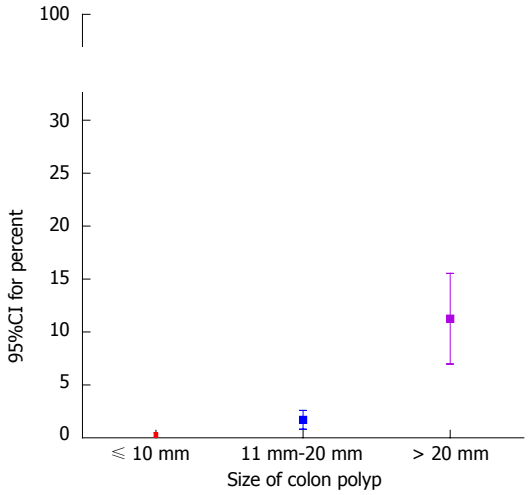

Figure 3 95%CI for percent of incomplete resection risk according to polyp size: size ≤ 10 mm, 95%CI: 0.07%-0.49%; 20 mm ≥ size > 10 mm, 95%CI: 0.82%-2.59%; size > 20 mm, 95%CI: 6.97%-15.52%.

Contrasting to polyps ≤ 10 mm, outpatient-based EMR for larger polyps can be challenging because of relatively high risk of delayed bleeding and immediate serious bleeding. The risk of delayed bleeding and serious immediate bleeding went beyond 2% and 5% in polyps between 10 mm and 20 mm. The risk rockets when the polyp size was over 20 mm; the risk of delayed bleeding went over 11%, and the risk of serious immediate bleeding exceeded 25%. Considering these results, we suggest doing EMR for patients with polyps no less than 20 mm in size with in-patient setting. We recommend meticulous prophylactic bleeding control for EMR site when polyps are more than 10 mm and no more than 20 mm. Furthermore, it would be beneficial to stress the possibility of hospitalization, if out-patient based EMR should be performed.

We calculated the efficacy of EMR according to polyp sizes. The risk of incomplete resection of a polyp ≤ 10 mm was 0.07% to 0.49%; the actual proportion of our center was 4/2061, and as the size increased, the risk of incomplete resection sharply increased. In our opinion, the range of incomplete polyp resection ≤ 10 mm was acceptable.

Because the sample size was too small in this study, it is difficult to determine whether chronic renal failure was a risk factor for delayed bleeding. However, considering the report that chronic renal failure was the risk factor of immediate bleeding[16] and based on many endoscopists' experience, this factor should be seriously considered.

There were several limitations to this study. In our center, we used standardized records for EMR to check each step of the procedure, complications, and management with endoscopic photos. However, it is possible that some information was incomplete or missed due to the characteristics of the retrospective design. Second, delayed bleeding with a long time interval could not be reported although the possibility of this occurring was

extremely low[17]. Finally, this study did not provide strong evidence for safety in regards to delayed bleeding in a real outpatient setting. The results from this report were obtained from in-patient data. For more solid evidence, prospective study in a real out-patient setting environment should be performed.

In the present investigation, we observed that the risks of delayed bleeding and serious immediate bleeding were very low for a polyp ≤ 10 mm. Moreover, the risk of incomplete resection was acceptable, according to the outlined condition. From these findings, we conclude that it is safe and acceptable to perform outpatient-based EMR for polyps no more than 10 mm.

COMMENTS

Background

Endoscopic mucosal resection (EMR) is widely performed in many clinical fields. Depending on the time of onset, cases of bleeding can be classified as either immediate or delayed. Delayed hemorrhages can be more serious because their onset is unpredictable and often occurs after hospital discharge. Although many endoscopists believe that it is safe to perform outpatient-based EMR for a polyp no more than 10 mm, no definite report about the possibility of delayed bleeding associated with specific conditions of alleged risk factors has been published.

Research frontiers

Depending on the time of onset, cases of bleeding can be classified as either immediate or delayed. Cases of immediate bleeding directly following the procedure can be easily managed with recent advancing endoscopic technology and hemostasis equipment, but delayed hemorrhages can be more serious because their onset is unpredictable and often occurs after hospital discharge. The size of the polyp was determined to be the most reliable factor for delayed bleeding. However, there has been no definite report about the actual possibility of delayed bleeding according to the sizes of polyps.

Innovations and breakthroughs

In the present study, the authors revealed that the risks of delayed bleeding and serious immediate bleeding were very low for a polyp ≤ 10 mm. Moreover, the risk of incomplete resection was acceptable, according to the outlined condition.

Applications

If the size of the polyp is no more than 10 mm, it would be desirable to perform outpatient-based EMR. Unless, inpatient-based practice might be needed to ensure safety of a patient regarding delayed bleeding.

Terminology

Delayed bleeding was defined by two conditions in this article. The first condition was when the patient experienced more than one episode of hematochezia at least one hour after EMR. The second condition was identifiable evidence of hemorrhage from an EMR site.

Peer review

This study is to evaluate the possibility of delayed bleeding according to specific situations of risk factors to understand conditions in which outpatient-based can be performed. This is very important study.

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OBSERVATIONAL STUDY

Practice patterns in FNA technique: A survey analysis

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Abstract

AIM: To ascertain fine needle aspiration (FNA) techniques by endosonographers with varying levels of experience and environments.

METHODS: A survey study was performed on United States based endosonographers. The subjects completed an anonymous online electronic survey. The main outcome measurements were differences in needle choice, FNA technique, and clinical decision making among endosonographers and how this relates to years in practice, volume of EUS-FNA procedures, and practice environment.

RESULTS: A total of 210 (30.8%) endosonographers completed the survey. Just over half (51.4%) identified themselves as academic/university-based practitioners. The vast majority of respondents (77.1%) identified themselves as high-volume endoscopic ultrasound (EUS) (> 150 EUS/year) and high-volume FNA (> 75 FNA/year) performers (73.3). If final cytology is non-diagnostic, high-volume EUS physicians were more likely than low volume physicians to repeat FNA with a core needle (60.5% *vs* 31.2%; $P = 0.0004$), and low volume physicians were more likely to refer patients for either surgical or percutaneous biopsy, (33.4% *vs* 4.9%, $P < 0.0001$). Academic physicians were more likely to repeat FNA with a core needle (66.7%) compared to community physicians (40.2%, $P < 0.001$).

CONCLUSION: There is significant variation in EUS-FNA practices among United States endosonographers. Differences appear to be related to EUS volume and practice environment.

Key words: Endoscopic ultrasound; Diagnostic procedures and techniques; Fine needle biopsy; Fine needle aspiration

Core tip: Endoscopic ultrasound with fine needle aspiration (EUS-FNA) has become a mainstay in the evaluation of various gastrointestinal diseases. However, little is known about the preferred FNA techniques used by practitioners. The aim of this survey study was to evaluate the practice patterns of a heterogeneous group of endosonographers. Subjects were queried in regards to training, experience, case volume, and preferences regarding FNA needle choice and techniques used. The results demonstrate a moderate variation in EUS-FNA practices among those endosonographers who responded to the survey (n = 210). Significant differences appear to be related to EUS volume and practice environment.

DiMaio CJ, Buscaglia JM, Gross SA, Aslanian HR, Goodman AJ, Ho S, Kim MK, Pais S, Schnoll-Sussman F, Sethi A, Siddiqui UD, Robbins DH, Adler DG, Nagula S. Practice patterns in FNA technique: A survey analysis. *World J Gastrointest Endosc* 2014; 6(10): 499-505 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i10/499.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i10.499

INTRODUCTION

Endoscopic ultrasound (EUS) with fine needle aspiration (FNA) has become a mainstay for the diagnosis of a variety of gastrointestinal diseases. Despite its widespread use, little is known about the preferred FNA techniques utilized by most practitioners. Numerous studies have attempted to address the relative importance of needle size, use of a stylet, use of suction, number of needle passes, and the use of rapid on-site evaluation of cytology (ROSE) as it relates to the effect on diagnostic yield of FNA[1,2]. Despite these studies, there is no consensus as to which techniques are preferred and most frequently practiced. In addition, it is unclear as to whether the level of experience of the endosonographer and the environment in which they practice has an impact on FNA technique. This information is relevant as differences in FNA technique may allow for analysis of one's own EUS practice, and afford an opportunity to assess if optimal techniques are being implemented for maximal diagnostic yield. The aim of this study was to ascertain current FNA technique by endosonographers with varying levels of experience from various practice environments across the United States.

MATERIALS AND METHODS

This study was designed as an electronic survey. Institutional review board approval was granted to conduct this research. Gastroenterology physicians who perform EUS-FNA in the United States were identified from a list of providers assembled by a major FNA needle manufacturer (Cook Medical Inc., Winston-Salem, NC). E-mail addresses were then queried *via* the membership directories of three major gastroenterology societies (American Society for Gastrointestinal Endoscopy, American Gastroenterological Association, and American College of Gastroenterology). Subjects were contacted through e-mail *via* a commercially-available electronic survey tool, and were asked to complete an anonymous electronic survey assessing their FNA practice. The survey was designed to be completed in less than 5 min. Emails requesting participation were sent out every two weeks to subjects who did not respond to the initial invitation to participate in the survey. There were no incentive programs utilized to increase the response rate. The survey was sent out between October 2011 and November 2011, and was closed after 5 wk.

High-volume EUS practitioners were defined as those physicians performing greater than 150 EUS examinations per year, medium volume defined as between 75-150 EUS exams per year, while low-volume EUS practitioners were defined as those physicians performing less than 75 EUS examinations per year. Recognizing that not all EUS practitioners perform FNA, we further stratified EUS practitioners by volume of FNA performed per year. High-volume FNA was defined as greater than 75 FNA per year, whereas low-volume was less than 75 FNA per year.

When defining FNA techniques, the term "needle pass" referred to one direct insertion of the needle across the GI lumen into the target lesion. The term "needle throw" was defined as one to-and-fro motion with the needle once it is already inside the target lesion.

Results of the survey were tabulated. Surveys with incomplete demographic information were excluded from the analysis. Blank responses to individual questions were excluded from the analysis of that question; no imputations were made for missing data. χ^2 analysis was used to assess associations between demographic variables and survey responses. A P value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS v16.0 (SPSS Inc., Chicago, IL) and Microsoft Excel 2010 (Microsoft Corp., Redmond, WA).

RESULTS

A total of 681 EUS-FNA practitioners were identified and contacted; a total of 210 (30.8%) completed the survey (Table 1).

Survey respondents

Most practitioners completed their GI fellowship training 3-10 years ago (n = 96; 45.7%) or more than 10 years ago (n = 76; 36.2%), while a small portion completed fellowship training within the past 3 years (n = 38; 18.1%). More than half of the respondents (n = 116; 55.2%) had received formal training in EUS during a 4th year advanced endoscopy fellowship. Just over half (n = 108; 51.4%) identified themselves as academic/university-based practitioners, while 48.6% (n = 102) were community-based.

The vast majority of respondents (n = 162; 77.1%)

Table 1 Characteristics of survey respondents

Category	*n* (%)
When training was completed	
< 3 yr ago	38 (18.1)
3-10 yr ago	96 (45.7)
> 10 yr ago	76 (36.2)
Fourth year fellowship	
Yes	116 (55.2)
No	94 (44.8)
Practice environment	
Academic/University-Based	108 (51.4)
Community Practice	102 (48.6)
Annual EUS volume	
25-75	14 (6.7)
75-150	34 (16.2)
> 150	162 (77.1)
Annual FNA volume	
< 75	56 (26.7)
> 75	154 (73.3)

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration.

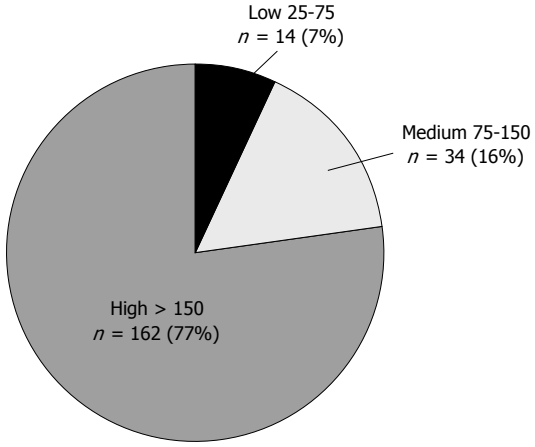

Figure 1 Distribution of survey responders based on endoscopic ultrasound volume.

identified themselves as high-volume EUS practitioners (> 150 EUS/year), compared to 16.2% (*n* = 34) medium-volume, with the remainder performing less than 75 EUS exams per year (Figure 1). With regards to FNA volume, 73.3% (*n* = 154) of respondents identified themselves as high-volume FNA practitioners (> 75 FNA/year) (Figure 2).

Needle type

When performing FNA of a solid pancreatic mass, the majority of respondents preferred to use a 22 gauge needle as their initial choice of needle (*n* = 130; 62%), compared to the 25 gauge needle (*n* = 80; 38.0%) or 19 gauge needle (0%, Figure 3). When performing FNA of a submucosal mass lesion in the esophagus, stomach, or rectum, the majority of respondents preferred the 22 gauge needle as their initial choice of needle (*n* = 149; 71.0), compared to the 25 gauge needle (*n* = 39; 18.6%), or the 19 gauge needle (*n* = 22; 10.5%, Figure 3). When performing FNA of a lymph node (mediastinal, abdominal, peri-rectal), respondents chose either the 22 gauge needle (*n* =106; 50.5%) or the 25 gauge needle (*n* = 98; 46.7%), with only 2.9% (*n* = 6) choosing a 19 gauge needle (Figure 3).

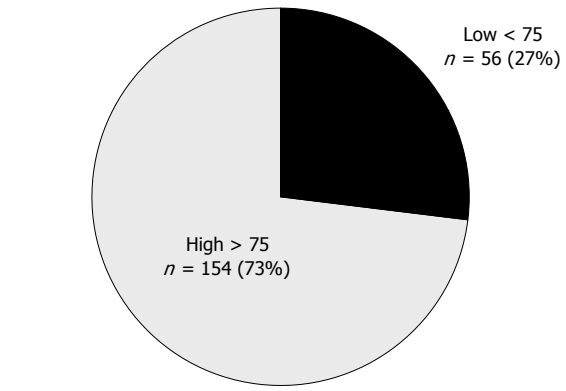

Figure 2 Distribution of survey responders based on fine needle aspiration volume.

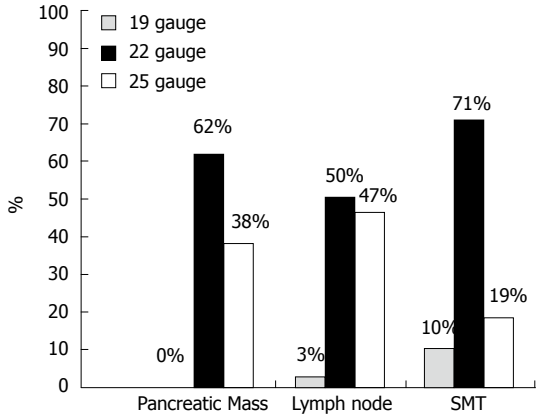

Figure 3 Needle size preference of survey responders based on lesion type. SMT: Submucosal tumor.

FNA technique

The vast majority of respondents reported an average of 3-5 needle passes (*n* = 173; 82.4%) when performing FNA of a solid pancreatic mass, while 13.3% (*n* = 28) reported performing 6 or more passes and 4.3% (*n* = 9) perform 1-2 passes.

For lymph nodes, 66.7% (*n* = 140) of respondents perform 3-5 needle passes on average, while 31.4% (*n* = 66) perform only 1-2 passes, and 1.9% (*n* = 4) perform 6 or more passes.

If ROSE is not available, over two-thirds of endosonographers (*n* = 140 out of 203 responses; 69.3%) will perform 3-5 passes, while 29.2% (*n* = 59) will perform 6 or more passes (Figure 4).

Once the needle tip is in the target lesion, 48.6% (*n* = 102) of respondents perform 10-20 needle throws, while 37.6% (*n* = 79) perform 6-10 needle throws, 8.6% (*n* = 18) perform more than 20 needle throws, and 5.2% (*n* = 11) perform 5 or less needle throws.

A stylet is used on the initial needle pass by 91.4% (*n*

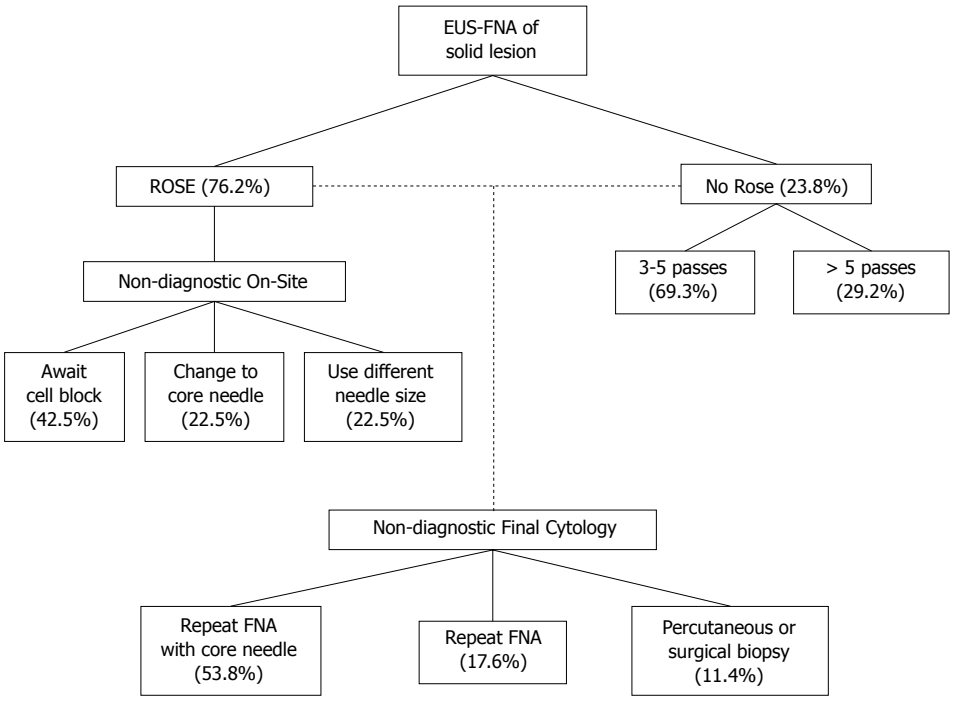

Figure 4 Endoscopic ultrasound with fine needle aspiration practice patterns of survey responders based on cytology results. EUS-FNA: Endoscopic ultrasound with fine needle aspiration.

= 192) of practitioners. On subsequent needle passes, the stylet is used by 81.8% (n = 171/209) of practitioners.

The routine use of suction was favored by 85.5% (n = 177/207) of respondents for FNA of solid lesions, and 66.8% (n = 140) of respondents for FNA of lymph nodes.

ROSE

The vast majority of respondents (n = 160; 76.2%) utilize ROSE when performing EUS-FNA (Figure 4). Of those practitioners using ROSE, 38.1% (n = 61) report that the specimen is read by an attending cytopathologist, 24.4% (n = 39) report that a cytotechnician examines the specimen, and 36.9% (n = 59) report that the specimen is analyzed by both. One subject (0.6%) reported self-review of the specimen as the main type of ROSE.

Decisions regarding inadequate/non-diagnostic specimens

If inadequate specimen is obtained as determined by ROSE, 42.5% (n = 68) of practitioners will cease performing further tissue acquisition and will await results of the cell block, while 22.5% (n = 36) change to core biopsy needle, 14.4% (n = 23) will change to a larger gauge FNA needle, and 8.1% (n = 13) will change to a smaller gauge FNA needle (Figure 4).

If a bloody specimen is obtained, 48.6% (n = 102) will continue FNA but without suction, while 23.8% (n = 50) will continue FNA but without any change in technique or needle size, 14.8% (n = 31) will continue FNA with both a change in needle size and without suction, and 3.3% (n = 7) will continue FNA with change in needle size only.

Decisions regarding non-diagnostic specimens

If the final cytology is non-diagnostic, 53.8% (n = 113) of subjects will repeat EUS-FNA and will consider using a core biopsy needle, 17.6% (n = 37) will simply repeat EUS-FNA, 7.6% (n = 16) will refer patient for a percutaneous biopsy, and 3.8% (n = 8) will refer patient for a surgical biopsy (Figure 4).

Group comparisons

Training: When comparing responses based on when training was completed, there was no statistical difference seen on all questions.

If adequate tissue was not obtained as determined by ROSE, those practitioners having completed a 4th year advanced endoscopy fellowship were more likely to switch to a core needle compared to those who did not complete a 4th year fellowship (28.0% *vs* 14.9%, P = 0.05). For the remainder of the questions, there was no statistically significant difference among the responses.

Practice environment: If the final cytology assessment was deemed non-diagnostic, academic-based physicians were more likely to repeat EUS-FNA and use a core biopsy needle, compared to community-based practitioners (66.7% *vs* 40.2%, P = 0.00012). For the remainder of the questions, there was no statistically significant difference among the responses.

EUS volume: If adequate tissue was not obtained as determined by ROSE, low/medium volume EUS practi-

tioners (< 150 EUS/year n = 20/35) were more likely to await results of the cell block compared to high-volume EUS practitioners (> 150 EUS/year, n = 40/125) (57.1% *vs* 32.0%, P = 0.04). High volume practitioners (n = 35) were more likely to utilize a core biopsy needle compared to low/medium volume practitioners (n = 1) (28% *vs* 2.6%, P = 0.002).

If the final cytology assessment was deemed non-diagnostic, high-volume physicians (n = 98) were more likely than low-volume physicians (n =15) to repeat FNA with a core needle (60.5% *vs* 31.2%, P = 0.0004). When compared to high-volume EUS physicians, low-volume EUS physicians were more likely to refer patients for a percutaneous biopsy (18.8% *vs* 4.3%, P = 0.0009) or a surgical biopsy (14.6% *vs* 0.6%, P = 0.000009). For the remainder of the questions, there was no statistically significant difference among the responses.

FNA volume: If adequate tissue was not obtained as determined by ROSE, low-volume FNA practitioners were more likely to terminate the procedure and await the results of the cell block as compared to high-volume FNA physicians (44.6% *vs* 27.9%, P = 0.006). High-volume FNA practitioners were more likely to use a core biopsy needle compared to low-volume FNA practitioners (23.4% *vs* 0%, P = 0.00006).

If the final cytology assessment was deemed non-diagnostic, high-volume FNA physicians were more likely to repeat FNA with a core needle, as compared to low-volume FNA physicians (59.7% *vs* 37.5%%, P = 0.004). When compared to high-volume FNA physicians, low-volume FNA physicians were more likely to refer to patients for a percutaneous biopsy (16.1% *vs* 4.5%, P = 0.005) or surgical biopsy (8.9% *vs* 1.9%, P = 0.02).

DISCUSSION

In an attempt to gain a snapshot of EUS practices and techniques, this electronic survey was distributed to endosonographers across the entire United States. Our results represent a cross-section of endosonographers as relates to their training, time in practice, and type of practice environment. This study demonstrates that there is variation in EUS-FNA techniques among EUS practitioners. In addition, we gain some insight into the volume of procedures performed, noting that the majority of respondents were considered high-volume, as based on our definition. Interestingly, but perhaps not surprising, a significant number of high volume endosonographers were community-based practitioners, which signifies the growth and acceptance of EUS beyond the tertiary referral center.

This study provides concrete data regarding practice patterns in actual clinical practice across a wide spectrum of endosonographers. For example, the 22-gauge needle appears to be the most popular needle used for FNA of solid pancreatic masses as well as submucosal tumors. This data is a bit surprising, as numerous randomized studies show no statistically significant difference in diagnostic yield between the 25-gauge and 22-gauge needles, but actually a trend towards better yield with the 25-gauge needle[3-5]. Furthermore, it is recognized that the use of the 25-gauge needle may actually pose a benefit when performing FNA of the pancreatic head or uncinate process, due to its flexibility and thus ease of use when compared to a higher gauge needle (1). However, we were not surprised to see that the 19-gauge needle was the least used needle for initial attempt at FNA. Still, despite these studies, 22 gauge needles appear to be overwhelmingly the needle of choice in most situations. Though our study did not address this specifically, we suspect that the associated technical difficulty of using the 19-gauge needle, particularly when performing trans-duodenal FNA for the pancreatic head/uncinate, and potential concerns about increased procedural risk (pancreatitis, bleeding, and perforation) are likely the reason behind this.

Survey responders favored the use of 3-5 needle passes for solid pancreatic mass lesions and for lymph nodes. The majority preferred a high number of needle throws as well (either 6-10 or 10-20). It is very interesting that nearly all responders utilized a stylet on the initial and subsequent FNA attempts, and nearly all used suction when performing FNA of a solid mass lesion. Two-thirds of respondents utilized suction when performing FNA on a lymph node. Numerous randomized trials have concluded that the use of a stylet increases the bloodiness of a specimen and ultimately does not improve the diagnostic yield in FNA[6-9]. Similarly, the use of suction has not been shown to enhance diagnostic yield in two randomized trials[10,11].

The ability to perform ROSE is perhaps the most important determinant of diagnostic yield when performing EUS-FNA. A number of studies have demonstrated that utilization of ROSE is associated with a significantly higher diagnostic yield, lower rate of indeterminate or unsatisfactory samples, and decreased number of needle passes[12-17]. Just over three quarters of respondents utilized ROSE when performing EUS-FNA. Interestingly, there was no difference in the utilization of ROSE between academic providers and those who considered themselves community practice based.

Perhaps the most relevant data from this study is the analysis of practice patterns amongst practitioners when a non-diagnostic specimen is obtained. Roughly one-half of respondents will repeat an EUS-FNA and consider obtaining a core biopsy at that time. Approximately 10% of respondents will not repeat EUS, but rather refer patients for either a percutaneous or surgical biopsy. Upon sub-group analysis, it appears that those practitioners who were either academic based, completed a 4th year advanced endoscopy fellowship, or were performed high volume EUS-FNA were significantly more likely to repeat an EUS-FNA and consider obtaining core biopsy. Low-volume practitioners, who were community based, were less likely to repeat endoscopic attempts at tissue acquisition and were more likely to refer for percutane-

ous or surgical biopsy. Knowing the overall safety and efficacy of EUS-FNA in general, this data may present an opportunity for low-volume and/or community based practitioners to re-evaluate their practice patterns when encountering a non-diagnostic specimen.

The main strength of our study is the novel attempt by our group to ascertain EUS practice patterns among a variety of endosonographers with diverse training backgrounds, experience, and practice environments. The high response rate (210/681, 30.8%) can purportedly be ascribed to the high level of interest and curiosity on practice patterns among practicing EUS physicians.

There are a number of limitations to our study. One major limitation is that of the inherent nature of survey studies with their associated recall bias. Another major limitation is the use of industry-supplied databases and society member lists to identify US endosonographers. This method most certainly did not identify every endosonographer eligible for participation in the study, and thus may introduce an element of selection bias in our study population. On the other hand, using this method did help identify over 600 eligible practitioners. The decision to use a database provided by a major needle manufacturer was based on the fact that at the time of this study, this company had the largest market share in the FNA needle market place, and was thus most likely to capture the largest number of endosonographers who perform FNA. Another limitation is that we did not inquire as to what region of the US our responders practiced in. There is a tendency for graduating trainees to practice in the region in which they completed their training. Thus, analysis of this aspect may have uncovered regional differences in practice patterns. This survey placed less emphasis on the use of core needle technology. During the time in which this survey was designed and implemented, newer reverse-bevel needle and large-gauge flexible needles were just being introduced into the marketplace, as were innovative changes in FNA technique (*e.g.*, capillary action by "slow pull" technique). Though we do assess utilization of core needles in some of our survey questions, we postulate that in the interim time frame since implementation of this survey, more endosonographers have had experience with these newer needle designs and FNA techniques, and thus we suspect that many endosonographers who have routinely adopted them in practice. Finally, we did not inquire as to each individual endosonographer's own rate of diagnostic yield and/or accuracy. Although this would be subject to tremendous recall bias, this information would give credence as to whether or not their preferred techniques are effective.

In conclusion, the results of this survey study of United States endosongraphers provides an opportunity for practitioners to examine their practice patterns, and compare their FNA technique to that of their peers. This may allow practitioners to identify areas for further self-education regarding implementation of evidence-based best practices. These results may help define a "standard" or preferred technique and could thus potentially be used as a reference point when designing prospective, comparative trials in EUS-FNA.

COMMENTS

Background

Endoscopic ultrasound with fine needle aspiration (EUS-FNA) has become a mainstay in the evaluation of various gastrointestinal diseases, in particular neoplastic mass lesions, both luminal and extraluminal. Despite its widespread use, little is known about the preferred FNA techniques used by practititioners.

Research frontiers

There are various types of FNA needles currently available. The main difference is in the size, or gauge, of the needle. The majority of the published data demonstrates that needle gauge does not seem to impact the success in obtaining sufficient tissue adequate to assess a diagnosis. Some needle types have the ability to obtain "core" biopsies of the target lesion, which allows for pathologic analysis (as opposed to cytologic analysis). Traditional core biopsy needles are cumbersome, and have been proven difficult to use under certain circumstances due to their rigidity and impact on the flexibility of the echoendoscope (*e.g.,* biopsies of the pancreatic head). Newer designs of the core biopsy hold promise in circumventing these issues, but their use in clinical practice remains unproven at this time. The aim of this current study was to assess the preferred FNA techniques and needle preferences among a large group of United States based endosonographers.

Innovations and breakthroughs

The results of this study demonstrate that there is moderate variation in EUS-FNA practices among EUS practitioners. Significant differences appear to be related to the volume of EUS performed by a particular physician, as well as whether they are based at an academic medical center as opposed to a community practice.

Applications

The results of this survey study of United States endosongraphers provide an opportunity for practitioners to examine their practice patterns, and compare their FNA technique to that of their peers. This may allow practitioners to identify areas for further self-education regarding implementation of evidence-based best practices. These results may help define a "standard" or preferred technique and could thus potentially be used as a reference point when designing prospective, comparative trials in EUS-FNA.

Terminology

EUS is an endoscopic procedure whereby a flexible tube with a video camera at its end is inserted through the mouth (or rectum) into the gastrointestinal tract. These scopes are equipped with a special ultrasound transducer at its tip, allowing for the performance of an ultrasound exam from within the gastrointestinal tract. This allows for detailed visualization of the wall layers of various gastrointestinal organs (*e.g.*, esophagus, stomach), as well as visualization of organs and structures immediately adjacent to the wall (*e.g.*, pancreas, lymph nodes). Fine needle aspiration (FNA) is a technique whereby a specially-designed needle is inserted through an accessory channel of the echoendoscope, and inserted directly into a target lesion under direct EUS guidance. The target lesion may be a lesion originating from within the gastrointestinal tract or be in an organ outside of the gastrointestinal tract. Cells obtained from FNA can be examined under the microscope for diagnostic purposes. Core biopsies refer to the ability to obtain "chunks" of tissue from the target lesion, allowing for microscopic analysis of not only cells, but the actual tissue architecture. This technique is often used when attempts at standard FNA have proven unfruitful.

Peer review

This is an electronic survey of eusonographers in the United States selected from a list provided by Cook Inc. with a response rate of approximately 30%.

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CASE REPORT

Role of preoperative endoscopic ultrasound-guided fine-needle tattooing of a pancreatic head insulinoma

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Abstract

Although insulinomas are rare, they are the most common pancreatic neuroendocrine tumor, with an incidence of four cases per million population. Insulinomas are generally benign indolent intrapancreatic tumors. Surgical resection remains the main option for treatment. However, up to 67% of a pancreatic head insulinomas are nonpalpable, thus surgical resection of the nonplapable insulinoma in this area could become problematic resulting in prolonged surgical time, increased risk of pancreatic duct injury and need for pancreaticoduodenectomy. Endoscopic ultrasound-guided fine-needle tattooing (EUS-FNT), has been shown to have a crucial role for localization of pancreatic body and tail lesions, facilitating laparoscopic distal pancreatectomy and helping surgeons identify the location of the tumor. EUS-FNT might have a role for preoperative localization of pancreatic head insulinomas which are likely to be nonpalpable. We report a case of preoperative EUS-FNT for localization of a nonplapable pancreatic head insulinoma. This report demonstrates that EUS-FNT of pancreatic head insulinomas may facilitate surgical resection, reduce operative time and decrease surgical complications.

Key words: Insulinoma; Endosonography; Endoscopic ultrasound-guided fine-needle tattooing; Pancreas; Neuroendocrine tumors

Core tip: Preoperative endoscopic ultrasound-guided fine- needle tattooing (EUS-FNT) pancreatic body and tail lesion has shown to decrease operative time and facilitate laparoscopic distal pancreatectomy. We reported that preoperative EUS-FNT can effectively help localizing non-palpable pancreatic head insulinoma, especially in deep pancreatic parenchymal tissue. EUS-FNT helps precisely localizing the tumor and avoiding pancreatic duct and vascular injury from surgery. Furthermore this technique may help in preserving normal pancreatic tissue, reducing operative time and most importantly minimizing risks of pancreaticoduodenectomy. EUS-FNT represents a safe and useful role for the preoperative localization and surgical planning of the pancreatic head insulinoma.

Leelasinjaroen P, Manatsathit W, Berri R, Barawi M, Gress FG. Role of preoperative endoscopic ultrasound-guided fine-needle tattooing of a pancreatic head insulinoma. *World J Gastrointest Endosc* 2014; 6(10): 506-509 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i10/506.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i10.506

INTRODUCTION

Endoscopic ultrasound (EUS) is a widespread imaging technique providing highly accurate localization of several pancreatic lesions. Endoscopic ultrasound-guided fine-needle tattooing (EUS-FNT) has been shown to have a role for localization of pancreatic body and tail lesions, facilitating laparoscopic distal pancreatectomy and helping surgeons identify the location of the tumor[1,2]. Although EUS-FNT has been widely used for localizing pancreatic lesions in the body and tail, the role of EUS-FNT for pancreatic head lesions has never been established or reported. We report a case of preoperative EUS-FNT for localization of a nonpalpable pancreatic head insulinoma.

CASE REPORT

A 70-year-old female, with history of hypertension and Parkinson's disease, presented to the hospital with neuroglycopenic symptoms, including confusion and weakness. A serum glucose level ranged between 22-65 mg/dL (normal: 73-107 mg/dL). She had persistent episodes of hypoglycemia which required aggressive intravenous dextrose replacement and ICU monitoring. Laboratory evaluation showed a C-peptide of 7.7 ng/mL (1.1-4.4 ng/mL), Insulin level of 20.9 MCiU/mL (0-20 MCiU/mL), Proinsulin of 19.9 pmol/L (3-20 pmol/L) and urine sulfonylurea screening was negative. Computer tomographic of the abdomen and pelvis with pancreas protocol revealed a 1.7 cm × 1.2 cm × 1.6 cm hypervascular lesion in the head of the pancreas located just medial to the gastroduodenal artery (GDA) and lateral to the superior mesenteric vein (SMV) (Figure 1). Endoscopic ultrasound (EUS) revealed a 15.5 mm hypoechoic, homogeneous tumor lesion in the head of pancreas. The tumor was adjacent to GDA and close to the pancreatic duct. EUS-guided fine-needle aspiration (EUS-FNA) biopsy was performed to confirm the diagnosis. Considering the location of the tumor in relation to the SMV and GDA, EUS-FNT was performed using a 22-gauge needle (Echo-Tip, Wilson-Cook). Two mL of sterile carbon-based ink (Spot; GI supply, Camp hill, PA) was injected slowly beginning in the center of the lesion and continuing until the needle exited the pancreas (Figure 2). Two days later, the patient underwent exploratory laparotomy. Intraoperatively, the insulinoma was nonpalpable and located deep in the pancreatic parenchyma between GDA and SMV. This was confirmed by intraoperative ultrasound. During dissection with bi-polar cautery between the GDA and the SMV, the preoperative tattooing was easily identified. The insulinoma was meticulously dissected with the guidance of the tattoo marker to preserve the pancreatic duct located posteriorly. During the procedure, the patient was given 10% dextrose water intravenously and blood sugar was checked every 15 min in order to prevent hypoglycemia. Finally, enucleation of the 2 cm pancreatic head insulinoma was performed without complication (Figure 3). Preoperative random insulin levels decreased significantly to10.6 MCiU/mL compared with preoperative insulin level of 23.8 MCiU/mL. Pathologic evaluation of the resected tumor revealed a pancreatic neuroendocrine tumor, consistent with an insulinoma. The patient had an uneventful postoperative hospitalization and remained euglycemic during outpatient follow-up at 6 mo.

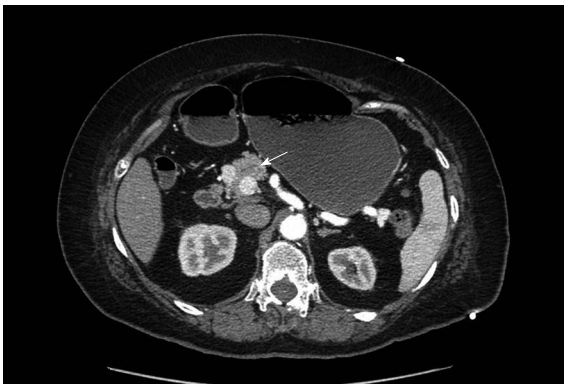

Figure 1 Computer tomographic of the abdomen and pelvis with pancreas protocol showed a 1.7 cm × 1.2 cm × 1.6 cm solid mass in the superior and right lateral margin of the head pancreas. The mass was hyperdense to the pancreas on early arterial phase imaging and became isodense with washout on more delayed phase images.

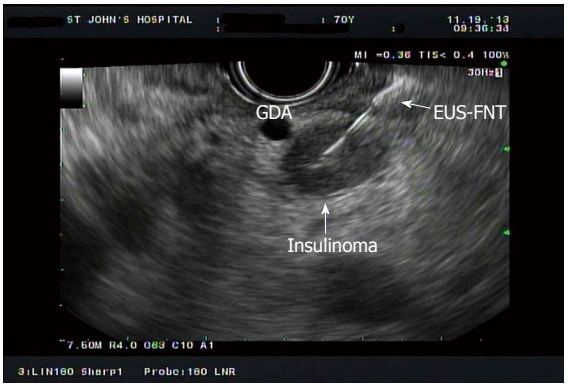

Figure 2 Endoscopic ultrasound-guided fine- needle tattooing image of a 15.5-mm hypoechoic mass located at pancreatic head adjacent to gastroduodenal artery.

DISCUSSION

After an insulinoma is diagnosed based on clinical and laboratory findings, surgical resection still remains the treatment of choice in the patient without metastasis. The type of surgical resection, which includes open or laparoscopic enucleation, pancreaticoduodenectomy and distal pancreatectomy are dictated by the location of the insulinoma. Therefore, methods for localizing insulinomas are very important. The preoperative localization of insulinoma which include CT, MRI and EUS, has a very high sensitivity 98%-100% especially after the widespread use of EUS[3,4]. In contrast, the rate of intraoperative detection, including intraoperative palpation and intraoperative ultrasound (IOUS) varies between studies, ranging from 83%-98%[3,5-8]. Hence, preoperative localization

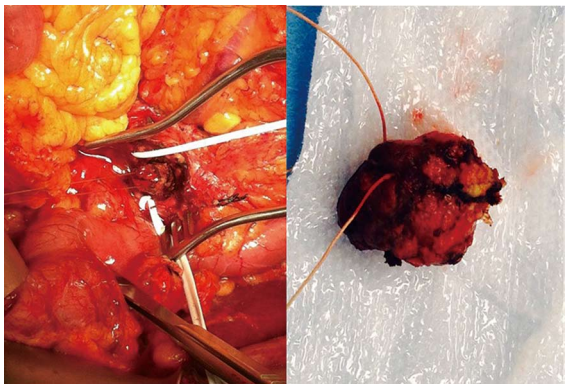

Figure 3 The tattooed insulinoma, located between gastroduodenal artery and superior mesenteric vein, was identified during operation (left). The 2 cm Insulinoma was enucleated without complication (right).

of the insulinoma is preferable and crucial for surgical planning and minimizing unnecessary surgery[3]. EUS, provides not only diagnosis by FNA biopsy but also localization of the tumor and has a sensitivity to detect neuroendocrine tumors ranging from 86% to 94%[4,9]. In general, EUS is recommended in patients with a high clinical index of suspicion where CT or MRI failed to localize tumor[3]. EUS-FNT accurately localizes small pancreatic tumors, facilitates identification of pancreatic lesions intraoperatively, and decreases operative time[10,11]. This was confirmed by studies that showed preoperative EUS-FNT of pancreatic body and tail lesions decreased operative time for laparoscopic distal pancreatectomy[1,2]. Although EUS-FNT has been widely used for localizing pancreatic lesions in the body and tail, the role of EUS-FNT for pancreatic head lesions has never been established or reported.

Even though surgery can a have minimal invasive approach, surgical resection of the insulinoma in the pancreatic head still may require an exploratory laparotomy and a pancreaticoduodenectomy (Whipple procedure) due to the structural complexity of this area. Thirty percent of insulinomas are located in the head and uncinate process of the pancreas[3,12]. There are reports that up to 67% of pancreatic head insulinomas are nonpalpable and 80% of nonpalpable insulinomas were located in pancreatic head[3,7]. This can result in a dilemma when intraoperative tumor localization fails and causes the need for unnecessary or extended blind resections. In 4 out of 61 patients from a case series, with and without preoperative EUS localization, a second operation was required to remove a tumor that was unidentifiable intraoperatively during the first operation[3]. Another study also showed that in 1 out of 26 patients, who underwent laparoscopic distal pancreatectomy (LDP) without EUS-FNT, required a second operation to remove the unidentifiable insulinoma by IOUS[2]. EUS-FNT appears to have a role for preoperative localization of pancreatic head insulinoma particularly in cases when a mass could not be palpable and identifiable even with IOUS during surgery.

EUS-FNA complications, include pancreatitis and infection, occur in approximate 0%-2.2%[13,14]. EUS-FNT is technically feasible and safe for pancreatic body and tail lesions. There is only a case of mild pancreatitis reported after EUS-FNT in a case series[1,2]. Since this is the first case report of EUS-FNT performed in the pancreatic head, our case demonstrates the safety of EUS-FNT in pancreatic head area. There was no evidence of pancreatitis or infection after the EUS-FNT procedure and during the intraoperative period.

Our report is the first to describe the use of EUS-FNT for the preoperative localization of a nonpalpable pancreatic head insulinoma. This case differs from previously described reports in the literature in several ways. First, the insulinoma, that we localized, was intraoperatively nonpalpable and located in the head of pancreas. Second, the patient had a moderate to large size tumor (1.55 cm) which was located very close to a major vessel and the pancreatic duct. EUS-FNT can play a role in precisely localizing the tumor margin, in the pancreatic head area, which can help facilitate surgery in nonpalpable insulinoma intraoperatively and helps avoid pancreatic duct and local vascular injury while preserving normal pancreatic tissue. Furthermore, it can help reduce operative time and most importantly decreases the chance for the need to perform pancreaticoduodenectomy.

In conclusion, EUS-FNT represents a useful and safe technique for the preoperative localization and surgical planning of the pancreatic head insulinomas. Further studies will need to be performed to confirm the efficacy and safety of EUS-FNT in the pancreatic head and confirm whether EUS-FNT of these pancreatic head lesions will be able to decrease the rate of pancreaticoduodenectomy and facilitate successful minimal invasive resection.

COMMENTS

Case characteristics

A 70-year-old female presented with neuroglycopenic symptoms and was found to have a pancreatic head insulinoma.

Clinical diagnosis

The patient who has insulinoma could present with either neuroglycopenic symptoms or adrenergic manifestations included shakiness, anxiety, nervousness, palpitations and sweating. Physical examination is usually unremarkable.

Differential diagnosis

Sulfonylurea-induced hypoglycemia, Insulin autoimmune hypoglycemia, Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS), other pancreatic neoplasms.

Laboratory diagnosis

Laboratory evaluation showed a C-peptide of 7.7 ng/mL (1.1-4.4 ng/mL), Insulin level of 20.9 MCiU/mL (0-20 MCiU/mL), Proinsulin of 19.9 pmol/L (3-20 pmol/L) and urine sulfonylurea screening was negative suggesting diagnosis of the insulinoma.

Imaging diagnosis

Computed tomography and Endoscopic ultrasound revealed a hypervascular lesion in the pancreatic head located just medial to the gastroduodenal artery and lateral to the superior mesenteric vein.

Pathological diagnosis

Pathologic evaluation of the resected tumor revealed a pancreatic neuroendocrine tumor. Immunohistochemistry staining is positive for synaptophysin, chromogranin and insulin, consistent with an insulinoma.

Treatment

The patient underwent exploratory laparotomy and enucleation of the 2 cm pancreatic head insulinoma without complication.

Related reports

Endoscopic ultrasound-guided fine-needle tattooing (EUS-FNT) has been shown to have a role for localization of pancreatic body and tail lesions, facilitating laparoscopic distal pancreatectomy and helping surgeons identify the location of the tumor.

Term explanation

Sterile carbon-based ink (GI Spot), is endoscopic non india-ink marker, contains high purity suspended carbon particles providing safe, proven, permanent endoscopic tattooing.

Experiences and lessons

This report demonstrates that EUS-FNT of pancreatic head insulinomas facilitate surgical resection, may reduce operative time and decrease surgical complications.

Peer review

It is an interesting case.

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CASE REPORT

Novel use of cap-assisted enteroscopy for detection of colorectal tumor in a patient with incarcerated inguinal hernia

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Abstract

Multiple reports have documented unsuspected inguinal hernias which result in difficulties during the colonoscopic examinations of patients. In most cases, the colonoscopy can be delayed until a surgical consult has further evaluated the inguinal hernia. This case report documents a patient who required a colonoscopy but surgical intervention for the detected inguinal hernia was not appropriate due to his co-morbid medical conditions. With the use of the combination of an enteroscope fitted with a cap and fluoroscopy, the inguinal hernia was able to be negotiated and the diagnosis of a cecal carcinoma was able to be confirmed.

Key words: Inguinal hernia; Cap-assisted colonoscopy; Cecal carcinoma; Fluoroscopy; Enteroscope

Core tip: Patients with inguinal hernias who are unfit for surgical repair but who have otherwise strong indications for colonoscopy are at risk of failed colonoscopy or an incarcerated colonoscope. This case study demonstrates that the use of a cap fitted to a more flexible enteroscope with fluoroscopic guidance can aid in the negotiation of the scope past the loops of bowel in the hernia sac.

Tan VPY, Wong IWC, Lee YT. Novel use of cap-assisted enteroscopy for detection of colorectal tumor in a patient with incarcerated inguinal hernia. *World J Gastrointest Endosc* 2014; 6(10): 510-512 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i10/510.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i10.510

INTRODUCTION

Patients with inguinal hernias are not uncommonly encountered by endoscopists performing colonoscopy. In patients with known large inguinal hernias or complicated inguinal hernias, including incarcerated hernias, surgical repair prior to colonoscopy is clinically indicated. However, in some circumstances, patients are unable to undergo surgical repair despite strong indications for the colonoscopy to be performed persisting. This case report demonstrates a strategy for facilitating the completion of a colonoscopy in such a patient.

CASE REPORT

A 79-year-old man with a history of severe aortic regurgitation and cardiac failure, presented with anemia and positive fecal occult blood testing. Gastroscopy was normal. A prior colonoscopic examination failed due to poor bowel preparation. He was referred for a second

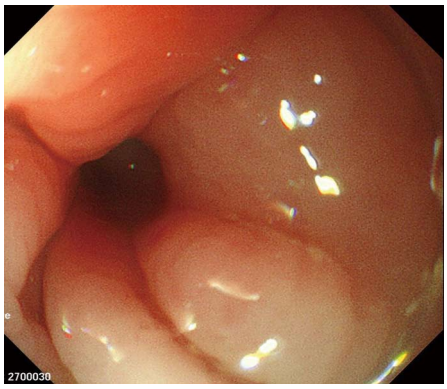

Figure 1 "Stricture" seen at sigmoid colon on initial colonoscopy.

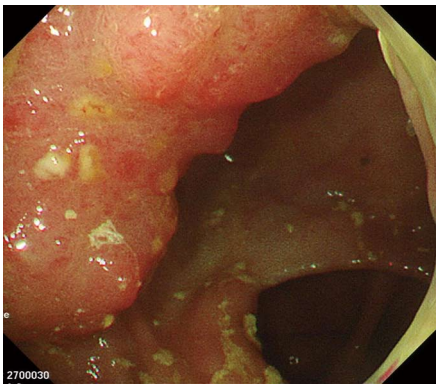

Figure 2 Cecal adenocarcinoma diagnosed using cap-assisted enteroscopy.

colonoscopy after polyethylene glycol preparation. During colonoscopy a "tight stricture" was encountered at the sigmoid colon. When the patient was turned, a large incarcerated left inguinal hernia was detected. The procedure was repeated with an enteroscope (Olympus SIF-Q260) fitted with a 4-mm cap at the tip, and under fluoroscopic guidance (Figure 1). Finally, with the aid of the cap, the scope negotiated through the acute bend inside the hernia sac and reached the cecum, where a large sessile tumor was found (Figure 2). Biopsies confirmed adenocarcinoma. No complication occurred during or after the procedure. The patient declined surgery due to his co-morbid conditions and died 3 mo later from cardiac causes.

DISCUSSION

Unexpected hernia detected during or after screening colonoscopy is not uncommon[1-5]. It may cause failure of the colonoscopy procedure[1-3] or result in a surgical emergency due to a colonoscopy induced strangulated bowel loop or incarceration[4,5]. Endoscopists should maintain a high index of suspicion when a "stricture" is seen in association with normal looking mucosa and consider whether a hernia could be a contributing factor. It is easy to detect the presence of inguinal hernia with proper exposure of the patient, however, for other types of hernia, fluoroscopic examination may be required[4,5]. In cases where an inguinal hernia is detected, colonoscopy should be delayed until a surgical opinion is sort however for cases where surgery would be inappropriate and colonoscopy still warranted, the use of fluoroscopic guidance can prevent inadvertent looping during scope passage through the hernia. The use of cap-assisted method, which had been shown to reduce colonoscopy failure rate[6], together with the use of a thin enteroscope contributed to the success of the examination.

COMMENTS

Case characteristics

A case of a patient with strong indications for a colonoscopy and an incarcerated inguinal hernia whose co-morbid medical conditions preclude surgical repair of the inguinal hernia.

Clinical diagnosis

The clinical diagnosis after cap-assisted colonoscopy performed with an enteroscope was cecal adenocarcinoma.

Differential diagnosis

Possible differential diagnoses include bleeding colonic polyp, bleeding colonic angiodysplasia and colonic neoplasms.

Laboratory diagnosis

Prior to the colonoscopy, the patient had iron deficiency anemia and fecal occult blood testing of his stools were positive.

Pathological diagnosis

A large sessile polyp suspicious for a neoplasm was seen in the cecum, which was biopsied and sent for histopathology confirming cecal adenocarcinoma.

Treatment

The patient declined surgery due to his co-morbid conditions that had precluded surgery for his inguinal hernia in the first place and died 3 mo later from cardiac causes.

Related reports

Negotiation through loops of bowel incarcerated in a hernia sac utilizing a cap fitted onto an enteroscope has seldom been reported in the literature, and is a useful strategy for endoscopists to consider when a similar circumstance presents itself.

Experiences and lessons

This case reports discusses a case where a patient had strong indications for a colonoscopy despite the presence of an incarcerated inguinal hernia, and presents a strategy utilizing a cap fitted to an enteroscope for facilitating the completion of the colonoscopy to enable the diagnosis of cecal adenocarcinoma to be made.

Peer review

This paper is helpful for clinical practice.

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REVIEW

Endoscopic ultrasound guided biliary and pancreatic duct interventions

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Abstract

When endoscopic retrograde cholangio-pancreatography fails to decompress the pancreatic or biliary system, alternative interventions are required. In this situation, endosonography guided cholangio-pancreatography (ESCP), percutaneous radiological therapy or surgery can be considered. Small case series reporting the initial experience with ESCP have been superseded by comprehensive reports of large cohorts. Although these reports are predominantly retrospective, they demonstrate that endoscopic ultrasound (EUS) guided biliary and pancreatic interventions are associated with high levels of technical and clinical success. The procedural complication rates are lower than those seen with percutaneous therapy or surgery. This article describes and discusses data published in the last five years relating to EUS-guided biliary and pancreatic intervention.

Key words: Endoscopic ultrasound; Endoscopic retrograde cholangio-pancreatography; Percutaneous transhepatic cholangiography; Bile duct; Biliary drainage; Pancreatic duct; Pancreatic drainage

Core tip: When endoscopic retrograde cholangiopancreatography fails or is not technically possible, endosonography guided cholangiopancreatography (ESCP) should be considered as the next potential intervention when the technical expertise is available. The increasing volume and quality of literature demonstrates that rendezvous procedures facilitated using ESCP are efficacious and safe. Other interventions are associated with greater complication rates and may be best undertaken only after multi-disciplinary discussion.

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INTRODUCTION

Therapeutic intervention in the common bile duct (CBD) or main pancreatic duct (MPD) is predominantly performed using endoscopic retrograde cholangiopancreatography (ERCP)[1]. Successful duct access is reported in over 95% of patients with unaltered anatomy[2-4]. Lower success rates are seen in patients with surgically altered anatomy[5,6] and neoplastic diseases[7] due to failure to access the duodenum (*e.g.*, surgical limbs, malignant stenoses) or more difficult duct access (*e.g.*, tumour overgrowth or high grade stricture). Where ERCP fails, alternative approaches for biliary or pancreatic decompression are required.

Radiological [percutaneous transhepatic cholangiography (PTC)] or surgical approaches (hepaticojejunostomy or choledochoduodenostomy) have traditionally facilitated biliary decompression when ERCP fails. However, the complication rates of these procedures are significantly higher than those seen with ERCP[2-4]. Surgical biliary decompression is associated with morbidity ranging

from 9%-67% and mortality of up to 3% in the post-operative period[8-11]. PTC is associated with significant complications in over 4% of cases and mortality in 1%-6%, although these figures are lower in patients with dilated biliary systems[12-16]. In addition, pain, infection, and drain care can lead to significant dissatisfaction after PTC with external drainage[15,17]. For pancreatic disease, there is no radiological procedure equivalent to PTC in the setting of failed pancreatic duct access. Percutaneous therapies for MPD stenosis[18], disconnected duct syndrome[19] and cutaneous pancreatic fistulae[20] have been described but are not commonly used. Consequently, in the setting of failed pancreatic duct access, management has been symptomatic or surgical.

Within this context, endosonography guided cholangiopancreatography (ESCP) was developed. The technique of endoscopic ultrasound (EUS) guided biliary access was initially described by Wiersema *et al*[21] who demonstrated a 70% success rate in performing EUS-guided cholangiography after unsuccessful ERCP. EUS guided drainage of the biliary system, using a transduodenal[22-24] or transhepatic approach[22,25] was subsequently reported. Similarly, initial descriptions of pancreatography performed using EUS[26,27] were followed by descriptions of therapeutic interventions[28,29]. These techniques overcome complications associated with external drains after PTC and/or the recovery time and morbidity associated with surgery.

The past 2 decades have seen numerous small case series reporting these procedures. This article describes large case series published in the last 5 years relating to EUS guided biliary and pancreatic intervention. Where necessary, these articles have been placed in context by referencing earlier studies.

NOMENCLATURE

Numerous terms have been utilized to describe the various techniques of EUS guided biliary or pancreatic intervention. The umbrella term "endosonography guided cholangio-pancreatography" (ESCP) was suggested and agreed upon by the majority of attendees during a recent consortium meeting[30]. The alternate term "endoscopic antegrade cholangio-pancreatography" was also discussed. The abbreviation ESCP will be used in this manuscript.

While the umbrella term remains to be standardized, only a limited variety of technical outcomes result from EUS-guided intervention[31]: (1) Biliary transpapillary drainage *via* intrahepatic access (with retrograde or antegrade stent placement); (2) Biliary transpapillary drainage *via* extrahepatic access (with retrograde or antegrade stent placement); (3) Biliary transmural drainage *via* intrahepatic access (hepaticogastrostomy); (4) Biliary transmural drainage *via* extrahepatic access (choledochoduodenostomy); (5) Pancreatic transpapillary drainage *via* pancreatic access; and (6) Pancreatic transmural drainage *via* pancreatic access (pancreaticogastrostomy).

Transmural drainage can be utilised with primary intent or as a salvage procedure where stenoses cannot be traversed to facilitate transpapillary drainage. The placement of a single drain with both transmural and transpapillary aspects is feasible and may reduce the risk of stent migration[32].

BILIARY INTERVENTION

Access to the biliary tree is required to manage benign and malignant biliary obstruction. ESCP can facilitate biliary decompression where ERCP has failed or is not feasible due to disease-associated pathologies (*e.g.*, malignant ampullary overgrowth, gastric or duodenal obstruction or a disrupted duct), the presence of anatomic variants (*e.g.*, duodenal diverticulum) or surgically altered anatomy (*e.g.*, Billroth Ⅱ resection or pancreaticoduodenectomy). ESCP is associated with greater technical success than precut papillotomy[33] and is reported to have similar or better efficacy, similar or fewer complications and, a similar or lower cost than PTC[34-36]. Furthermore it may be safer than PTC in certain disease processes (*e.g.*, obesity or ascites) or where a delay between PTC guidewire placement and endoscopic rendezvous is foreseen[37].

Biliary access

Biliary ESCP may be performed using an intrahepatic or extrahepatic approach. However only one point of access is technically feasible in the majority of cases[31]. Therefore, imaging studies and prior endoscopies should be comprehensively reviewed prior to commencing the procedure. The technical aspects of both approaches have been described comprehensively elsewhere[32,38-40] but will be described briefly.

Intrahepatic access to the biliary system is approached from the cardia or the lesser curve of the stomach. From these locations, the left lobe of the liver is scanned to identify a dilated bile duct in an orientation which will facilitate both the initial needle puncture as well as the passage a guidewire and other accessories as needed. A fine needle aspiration (FNA) needle is passed into the biliary system and bile aspiration performed to confirm the intraluminal location of the needle tip. A cholangiogram is then performed under fluoroscopy to define the local anatomy and a guidewire then passed into the biliary system.

The extrahepatic approach offers two advantages above the intrahepatic route: (1) access to a dilated CBD or common hepatic duct is often easier in patients with low CBD or ampullary obstruction; and (2) the retroperitoneal location allows safe access in patients with ascites. For an extrahepatic approach the ultrasound transducer is placed in the duodenal bulb or in the second part of the duodenum. Both ultrasound and fluoroscopic assessment are used to identify a point (either intrapancreatic or suprapancreatic) where, after needle puncture of the bile duct, the guidewire is likely to progress in the desired direction. If transpapillary drainage is desired, the echo-

endoscope should be placed in a short-scope position to facilitate passage of the guidewire in an anterograde fashion toward the ampulla[40,41]. For transmural drainage, the echoendoscope should be in the long-scope position to promote retrograde passage of the guidewire into the intrahepatic system[42]. An FNA needle is passed into the biliary system and aspiration performed to confirm the intraluminal location of the needle tip. A cholangiogram is then performed under fluoroscopy to define the local anatomy. Under fluoroscopic guidance a guidewire is then passed into the biliary system.

Biliary drainage

Transpapillary: When transpapillary drainage is desired, the guidewire is passed through the site of obstruction and into the duodenum. Advancement of the guidewire to the ampulla may be more difficult during the intrahepatic approach as the wire may pass into other branches of the biliary tree. If a rendezvous procedure[41,43-45] is desired, a sufficient number of loops of guidewire are left in the small bowel to reduce the risk of wire dislodgement while the echoendoscope is removed from the patient. A standard duodenoscope can be used to complete the procedure in patients with native gastroduodenal anatomy. An extended forward-viewing instrument (colonoscopy or enteroscope) is needed for patients with an afferent jejunal limb or Roux-en-Y reconstruction following pancreaticoduodenectomy. An alternative strategy is to use the therapeutic echoendoscope to place a transpapillary biliary stent in an antegrade fashion after dilation of the transmural access tract.

Transmural: Where it is not possible to traverse an obstructing biliary lesion, transmural stent placement may be performed for biliary drainage[46]. This approach may also be deliberately chosen in order to facilitate stent changes where long term drainage is needed (*e.g.*, in patients with altered anatomy or duodenal stenosis). After biliary access is secured with a guidewire, a dilating balloon, dilating catheter, or needle knife is inserted in an antegrade manner, over the guidewire, to dilate the tract. Subsequently, a stent is deployed transmurally with drainage into the stomach or duodenum. As neither the liver nor the common bile duct is adherent to the intestinal wall, transmural drainage carries the risk of bile leak or pneumoperitoneum.

Technical success

Twelve large case-series or prospective trials regarding biliary ESCP have been reported in the last five years (Table 1). The biliary system was successfully accessed in 97%-100% of cases. Where specifically reported, biliary access *via* the intrahepatic and extrahepatic approaches was 100%. Reasons for access failure include failure to access the peripheral hepatic duct[46], non-dilated hepatic ducts[47], or surgically altered anatomy[47].

Successful biliary drainage was reported in 44%-100% of cases; 44%-100% using intrahepatic access, and 81%-100% using extrahepatic access. Drainage was precluded by failure to successfully pass a guidewire through tortuous intrahepatic ducts[46], failure to traverse a stricture with the guidewire[41,46] or unsuccessful dilation of the access tract[48]. A guidewire was passed into the small bowel in 57%-100% of cases through an extrahepatic approach[46,49], and 44%-94% of cases using an intrahepatic approach[41,49]. In the series by Maranki *et al*[46] 13% of intrahepatic approaches were converted to extrahepatic approaches, primarily due to failure to pass the guidewire to the point of obstruction. Once transpapillary placement of a guidewire is achieved, retrograde placement of a transpapillary biliary stent is possible using a rendezvous approach. The alternative antegrade transpapillary or transluminal stent placement requires dilation of the transmural access tract. Intrahepatic access results in a lower success rate of transpapillary drainage[41,49]. For transmural drainage, technical success rates of over 95% have been reported for both intrahepatic and extrahepatic approaches[48,50].

Where "real world" approaches have been described, the reported success rates are similar[47,51,52]. Shah *et al*[47] reported EUS guided interventions where the desired outcome was rendezvous procedure or antegrade transpapillary stenting when the ampulla was not accessible. Although the final point of access utilized was not specified, the overall success rate for decompression was 85% (58 of 68 patients). As biliary access was achieved in 68 of 70 (97%) of cases, a higher technical success rate was feasible if transmural drainage had also been used. Park *et al*[51] demonstrated a success rate of 91% (41/45) in a prospective trial utilizing a mixture of rendezvous procedures, antegrade stent placement, transmural drainage or repeat ERCP. In this study 8 of 12 patients in whom the initial procedure failed successfully underwent an alternate ESCP intervention, 2 patients underwent repeat ERCP and 2 patients were referred for PTC. In an earlier trial by the same authors, a 100% technical success rate for extrahepatic drainage was seen when 2 patients who underwent "salvage" rendezvous ERCP were included[50]. However, in contrast, in a Spanish cohort, where a variety of approaches were used, technical success was reported in only 69% of cases[52].

Functional success on a per-protocol basis (defined as a > 75% reduction in bilirubin within one month after the successful placement of a stent) was 87% by transmural intrahepatic drainage and 92% by transmural extrahepatic drainage in the prospective series reported by Park *et al*[50]. Overall functional success rates of > 95% following technical success have been described elsewhere[51,53].

Procedure related complications

ESCP related complications were reported in 3%-34% of cases (Table 1). The most commonly reported adverse events include infections (cholangitis), pain, pneumoperitoneum, bile leak, and bleeding. Although the choice of transpapillary or transluminal drainage does not appear to

Table 1 Summary of recently published reports of endoscopic ultrasound-guided biliary interventions including > 35 patients

Ref.	*n*	Access point	Stent placement			Successful drainage *n* (%)	Complications		Notes
			TP		TM		*n* (%)	Type	
			RV	AG					
Maranaki *et al*[46] 2009	49	IH	-	26[a]	3	29/40 (73%)	8/49 (16%)[b]	Pneumoperitoneum (4)	Retrospective
		EH	-	8	4	12/14 (86%)		Biliary peritonitis (1)	Five patients converted from IH to EH and have been included here to demonstrate success *via* access point (IH *n* = 40, EH *n* = 14)
								Bleeding (1)	
								Aspiration pneumonia (1)	Overall technical success of drainage 41/49 patients (84%)
								Abdominal pain (1)	[a]Includes one antegrade placement of intra-ductal stent and 1 balloon dilation of stricture (*i.e.*, the stricture was traversed by the guidewire)
									[b]Complication rate per patient (IH *n* = 5, EH *n* = 3)
Park *et al*[50] 2011	57	IH	-	-	31	31/31 (100%)	11/57 (19%)	Pneumoperitoneum (7)	Prospective follow up
		EH	2	-	24	26/26 (100%)		Biliary peritonitis (2)	Primary procedural aim was transmural stenting. A rendezvous technique was successfully utilized in 2 patients with malignant disease in whom TM EH stenting was not possible
								Bleeding (2)	
									All 6 patients with benign strictures had previously failed an EUS guided rendezvous procedure
Vila *et al*[52] 2012	106	NS	NS	NS	NS	73/106 (69%)	24/106 (23%)	NS[c]	Retrospective case series pooling biliary and pancreatic intervention: 19 hospitals, 23 endoscopists, 106 biliary and 19 pancreatic interventions
									[c]Complications were not specified by procedure type. Of the 29 complications among the biliary and pancreatic interventions 5 were managed endoscopically, 3 with percutaneous intervention and 2 were managed surgically
Shah *et al*[47] 2012	70	NS	39		19	58/76[d,e] (76%) Procedures	6/76[d,e] (8%) Procedures	Pancreatitis (2)	Retrospective
								Hematoma (1)	Complications include those from ERCP attempted prior to ESCP
								Bile leak (1)	
								Infection (1)	[d]In 2 patients intervention was deemed unnecessary after cholangiography. Crossover between antegrade stenting and rendezvous procedure was allowed freely; 6 patients failed rendezvous and were treated successfully by an antegrade EUS intervention, 2 patients failed direct EUS guided therapy and successfully underwent a ESCP rendezvous procedure. Therefore 76 procedures were performed with therapeutic intent
						58/68[d,e] (85%) Patients	6/70[d,e] (9%) Patients	Duodenal perforation (1)	
									[e]Success and complication rates are described on a "per procedure" and "per-patient" basis as some patients had more than one procedure
Iwashita *et al*[41] 2012	40	IH	4	-	-	4/9 (44%)	5/40 (13%)	Pancreatitis (2)	Retrospective
		EH	25	-	-	25/31 (81%)		Abdominal pain (1)	Only rendezvous procedures attempted. No transmural drainage or antegrade stenting
								Pneumoperitoneum (1)	Overall technical success in 29/40 patients (73%)
								Fever, subsequent death (1)	Technical failure due to inability to pass guidewire to small intestine in 11 patients (27%)
Dhir *et al*[33] 2012	58	EH	57	-	-	57/58 (98%)	2/58 (3%)	Contrast leakage (2)	Retrospective
									Only rendezvous procedures attempted. No transmural drainage or antegrade stenting
Dhir *et al*[49] 2013	35	IH	16	-	-	16/17 (94%)	12/35 (34%)	Pain (7)	Retrospective
		EH	18	-	-	18/18 (100%)		Bile leak (2)	Only rendezvous procedures attempted. No transmural drainage or antegrade stenting
								Pneumoperitoneum (2)	Overall technical success in 34/35 (97%)
								Pain (1)	Failure due to inability to traverse obstruction with guidewire
									11 (of 12 total) complications occurred in the TH cohort
Park *et al*[51] 2013	45	NS	NS	NS	NS	41/55[f] (75%) Procedures	5/55[f] (9%) Procedures	Pancreatitis (1)	Prospective observational cohort study
								Biliary peritonitis (1)	Mixture of rendezvous procedures, antegrade stent placement, transmural drainage or repeat attempt at ERCP. Significant crossover during procedures depending on clinical scenario; 10 patients underwent an alternate interventional strategy after the initial procedure failed
								Pneumoperitoneum (1)	
						41/45[f] (91%) Patients	5/45[f] (11%) Patients	Stent Migration (1)	
								Biloma (1)	
									[f]Success and complication rates are described on a "per procedure" and "per-patient" basis as some patients had more than one procedure

Khashab *et al*[53] 2013	35	IH	2	-	5[g]	33/35 (94%)	4/35 (12%)	Pancreatitis (1) Pneumoperitoneum (1) Retained sheared wire (1) Acute cholecystitis (1)	Retrospective An initial attempt using a rendezvous technique was followed by a transluminal approach if rendezvous failed [g]Two patients had trans-esophageal stents placed
		EH	11		15				
Gupta *et al*[80] 2014	240	IH	NS	NS	NS	132/145 (90%)	81/238 (34%)	Bile leak (27) Bleeding (26) Pneumoperitoneum (12) Cholangitis (11) Abdominal pain (5) Stent occlusion (2)	Retrospective Data reported here as they are in the paper; internal consistencies in data reporting without explanation make this data difficult to interpret Overall technical success reported in 87% of patients 52 (of 146, 36%) complications in the IH group and 29 (of 89, 33%) in the EH group
		EH	NS	NS	NS	75/89 (84%)			
Kawakubo *et al*[48] 2014	64	IH	-	-	19	19/20 (95%)	12 (19%)	Bile leakage (5) Stent misplacement (3) Bleeding (2) Pneumoperitoneum (1) Cholangitis (1) Biloma (1) Perforation (1)	Retrospective Only Transmural procedures attempted Transpapillary stent placement had been performed prior to ESCP in 31 (48%) patients Two failures in EH group due to failure to dilate tract. One failure in IH group due to failure to access non-dilated bile duct Six complications were reported in each group. Two stents deployed intra-peritoneally during IH TM drainage. One plastic stent migrated and resulted in perforation
		EH	-	-	42	42/44 (95%)			
Dhir *et al*[54] 2014	68	IH	NS	NS	NS	34/36 (94%)	17/68 (25%)	Cholangitis (5) Bile leak (4) Death (3) Perforation (2) Pneumoperitoneum (2) Bleeding (1)	Retrospective 20 patients underwent rendezvous procedures, 35 underwent direct EUS guided intervention (AG TP or TM). IH approach used in 34 procedures and EH approach in 31 procedures Overall technical success reported in 65/68 (87%) of patients
		EH	NS	NS	NS	31/32 (97%)			

Superscripts refer to specific comments in the "Notes" column. AG: Antegrade; EH: Extrahepatic; ESCP: Endosonography guided cholangiopancreatography; EUS: Endoscopic ultrasound; IH: Intrahepatic; NS: Not specified; RV: Rendezvous; TM: Transmural; TP: Transpapillary.

affect the complication rate[54], many reported complications can potentially be attributed to the mural defect associated with ESCP. The intestinal wall is not adherent to either the liver or the CBD. This facilitates the potential leakage of intestinal or biliary luminal contents into the peritoneum or the retro-peritoneal space. The intrahepatic technique is associated with a higher risk of complications[54]. Consequently, the extrahepatic approach should be considered preferential where a patient's anatomy and disease allow. Covered metal stents may reduce the risk of bile leakage where transmural stenting is performed[48] but the use of these stents may be precluded by smaller receiving bile ducts. The most significant predictor of complications identified to date is the use of a needle-knife to dilate an access tract during ESCP (odds ratio 12.4)[50]. Bougie dilators or dilating balloons should be preferentially used where possible. Procedural failure and male patients are associated with a higher risk of complications but these risk factors cannot be altered[52]. In view of these potential complications, patients should be monitored closely and a low threshold for investigation and intervention adopted. When complications occur, the majority can be managed conservatively.

A 3% mortality associated with biliary ESCP has been reported[54] and 4% mortality reported in pancreaticobiliary ESCP[52]. The majority of ESCP associated deaths are associated with biliary, rather than pancreatic, interventions. This may represent publication bias and/or the proportionally greater number of procedures performed in the biliary tract.

One prospective trial of 25 patients demonstrated that the complication rates of PTC and ESCP appear similar[34]. A subsequent retrospective report found ESCP to be superior to PTC for both technical success and complications[35]. The most recent retrospective comparison suggests that functional success rates of ESCP and PTC are similar but that complication rates and cost are lower for ESCP[36]. No trials have compared EUS-guided intervention to surgery but based on historical data the complication rates of ESCP are lower[8-11].

Stent dysfunction

Follow up data regarding stent dysfunction (occlusion or migration) is reported in few of the series described in Table 1. Park *et al*[51] identified no stent dysfunction among 41 successfully placed stents during a mean follow up period of 165 d (range 30-275 d). Khashab *et al*[53] identified only 2 stent dysfunctions among nine patients followed up for a mean of 276 d (one transluminal metal stent occlusion at 42 d and one transpapillary metal stent migration at 62 d). The remaining 24 patients in this series died as a consequence of their diseases, without stent dysfunction, after a mean of 90 d. In a prospective follow-up study of transmural stenting Park *et al*[50] estimated mean stent patency for intrahepatic and extrahepatic stents of 132 and 152 d respectively using a Kaplan-

Meier method[50]. Kawakuba *et al*[48] similarly reported no significant difference in rate of stent dysfunction between intrahepatic and extrahepatic groups but 25% of the transmural extrahepatic stents and 32% of the transmural intrahepatic stents malfunctioned (mean time to dysfunction of 103 d and 62 d respectively). In all of these studies, a variety stent types were used but subgroup analyses were infrequently reported. However, in previous smaller studies, with cohorts of three to six patients, similar results have been reported in more homogeneous groups[55-59].

The heterogeneity of techniques and stents used makes firm conclusions difficult to report. However, for transpapillary stents, either metal or plastic, patency is expected to be similar to those deployed during ERCP for similar indications[60-63]. Although no prospective comparative studies exist, a metal stent with a larger diameter is expected to offer longer lasting patency than that of a plastic stent in biliary ESCP procedures.

Where dysfunction does occur, stent exchange is required. After tract maturation (estimated to take 2 to 3 wk), the stent can be removed, the fistula re-cannulated and a new stent placed. Where stent malfunction occurs before tract maturation, or where access is more tenuous, a snare-over-the-wire technique can be utilized to safeguard biliary access[64].

Limitations of data regarding biliary ESCP

ESCP has proven efficacy in successfully treating biliary diseases. Recently published literature (Table 1) describing large case series has refined our understanding of the technical success and complication rates of these procedures. However, significant limitations within the data still exist.

Firstly, the indications for performing ESCP rather than PTC or surgery are not defined. Furthermore, as the reported data represents a heterogeneous mixture of benign and malignant processes, the outcomes by disease type are not clear. However, ESCP to facilitate retrograde access to the biliary system is associated with an acceptable complication rate when considered as an alternative to PTC or surgery. Where short term palliation is needed and transpapillary drainage is not possible, transmural drainage by ESCP (particularly *via* the extrahepatic route) and PTC offer equivalent technical success with shorter hospital stays than surgery[8-9,34-35,49,65]. However, ESCP offers a single stage procedure which does not require an external biliary drain; factors which may be very important to those with limited life expectancy. Where prolonged decompression of the biliary system is required (*e.g.*, benign conditions refractory to management or malignancy), surgery may be more appropriate than transpapillary stenting as fewer follow up interventions are required[11,65]. In the absence of trials directly comparing surgery with transmural ESCP for benign and malignant disease, the decision in whom to perform ESCP must be made on an individual basis.

Secondly, there are limited prospective data regarding the "real world" technical success of ESCP. Although prospective data have demonstrated very high rates of technical success, this reflects the experience of a single operator[50,51]. Where multicentre retrospective series are described, the success rates are more variable[48,52]. As second attempt ERCP may be more successful in referral centres when the ampulla is accessible[3-4], it seems appropriate that ESCP should be performed only in these locations after a second attempt at ERCP has failed. An alternative strategy may be that after a failed second ERCP in local centres, ESCP to facilitate a rendezvous procedure is attempted, followed by referral to a specialist centre if this fails. This approach is supported by two factors: (1) technical success and complication rates do not appear to be associated with the operator's EUS experience or the location at which the procedure is performed[48,52]; and (2) second attempt ESCP may be successful where the initial procedure has failed[66].

Finally, data are lacking regarding the optimal approach to use during ESCP. Extrahepatic approaches and metallic stents are associated with fewer complications but data from well designed prospective randomized controlled studies comparing the long term success of each are lacking. However, as the majority of patients undergo ESCP for malignant disease, a single procedure, achieving functional success for short term palliation, may be sufficient for these patients and offers the advantage of not having to manage an external biliary drain or surgical wounds.

PANCREATIC INTERVENTION

Symptoms associated with chronic pancreatic disease are thought to be associated with MPD pressure[67,68]. ERCP mediated "decompression" of the MPD has been used to successfully treat recurrent acute pancreatitis, chronic pancreatitis associated with MPD stones or strictures, MPD disruption, pancreatic fluid collections and pancreatico-enteric anastamotic strictures[1]. ESCP can facilitate pancreatic intervention when ERCP fails. In addition, it provides a non-surgical approach to the management of disconnected duct syndrome.

Pancreatic duct access

The MPD can be visualised throughout its length from the gastric body or the duodenal bulb. The point of access is chosen based on the location of ductal disruption or obstruction. The MPD access point should have minimal intervening pancreatic parenchyma and be orientated to allow needle access, guidewire passage, tract dilation, and stent placement if needed[69]. After puncture of the MPD using an FNA needle, position is confirmed by contract injection to obtain a fluoroscopic antegrade pancreatogram. Access to ducts of 1mm diameter is possible and has been used to facilitate rendezvous procedures[70,71] but for transmural drainage a larger diameter duct is recommended[72]. In cases where ERCP has failed due to inability to identify the papilla injection of methylene blue with the radio-opaque contrast into the MPD is usually sufficient to allow papillary identification and

successful ERCP[73]. Where pancreatic intervention failed because of MPD obstruction, a guidewire is advanced under fluoroscopic vision through the MPD and into the duodenum to allow retrograde access to the MPD. Where the guidewire cannot traverse the papilla, transmural intervention may be considered. Transmural interventions require dilation of the access tract.

Technical success

Larger case series from the last five years have demonstrated successful pancreatic duct access in 78%-100% of cases (Table 2). Success rates are lower when the pancreatic duct is of normal calibre (57% *vs* 100% with a dilated MPD)[73]. Successful passage of a guidewire though the papilla is reported in 33%-88% of cases[73,74]. Transpapillary guidewire passage may not be possible due the tendency of the guidewire to pass into pancreatic side branches, difficulty positioning the echoendoscope in an orientation to allow antegrade passage of the guidewire or a high grade stricture[73]. Pre-procedural assessment of stenotic severity is not a predictor of successful guidewire passage[71]. In select cases (pancreaticojejunostomy strictures post Whipple's procedure), the use of a needle-knife, passed antegrade through the MPD to the stricture, can increases the success rate of guidewire passage[75]. However, among the three patients reported in this series, one developed pancreatitis suggesting a possible high rate of complications. Where transpapillary passage of the guidewire fails, the placement of a transmural stent is feasible.

Technical success (*i.e.*, the placement of a stent for pancreatic decompression) has been reported in 45% to 88% of procedures. Series in which either rendezvous or transmural stenting were employed report higher success rates (Table 2). In the largest series reported to date (43 patients), the technical success rate per procedure was 70% for therapeutic intervention[71]. Although one of the proposed advantages of ESCP is that it can be performed in the same session as failed ERCP, this approach was associated with a lower rate of technical success[71].

Interestingly, although Kikuyama *et al*[66] described initial technical success in only 6 of 14 (38%) patients with surgically altered anatomy undergoing EUS guided pancreatic interventions, a repeat attempt resulted in success in another 5 (of 8) patients. This suggests that similar to ERCP, repeat attempts at ESCP may yield higher success rates.

Among those who are successfully stented, the long term success rates are high and durable. Fujii *et al*[71] demonstrated significant clinical response after 12 mo. Among 29 (of 32) patients available for follow up at median 37 mo (range 12-72 mo), 70% of patients had complete symptom resolution[71]. Symptoms were better controlled while an MPD stent was in situ (83% complete symptom resolution); during follow up after stent removal (median of 32 mo) symptom recurrence occurred in 4 of 23 patients at a median 14 mo. Benign anastomotic strictures and longer stents were associated with a lower likelihood of a complete symptomatic response in a univariate analysis. Overall, these data are similar to previously reported pancreatic ESCP data[29,72,76]. Providing objective evidence for these findings, among patients who have stents successfully placed, the MPD diameter decreases suggesting resolution of MPD hypertension[29,71,76].

Complications

Complications were reported in 6%-33% of procedures; serious complications are less frequent. In the largest reported series, the complication rate was significantly increased by the inclusion of "abdominal pain" which resolved without any intervention[71]. Other lager case series have reported serious complication rates of 8%-13%, predominantly pancreatitis[47,72,76]. Although leakage of pancreatic fluid after tract dilation is a frequently cited technical concern, it was infrequently reported in these cohorts. However, the use of a needle-knife for tract dilation and duct access should be avoided where possible in order to minimize the risk of complications.

Stent patency

Stent occlusion and migration represent the predominant concern during long term follow up. Stent dysfunction is estimated to occur in over 50% of patients with long term stents[72,76]. The median time until stent dysfunction is estimated to be 5-6 mo[72,76]. However, it must be noted that this represents reporting of a heterogeneous groups of stents.

Limitations of data regarding pancreatic ESCP

As few percutaneous therapies are available for pancreatic intervention, there is a significant void which ESCP can fill. In patients with surgically altered anatomy, ERCP has high failure rates[5,77]. When the alternative is surgery, ESCP offers a relatively lower risk therapy for these patients. In situations where the papilla is accessible to ERCP, a pancreatography alone may be sufficient to allow successful pancreatic intervention and should therefore be considered, even without the need for a rendezvous procedure[73].

However, similar to the biliary ESCP data, heterogeneity among cohorts makes conclusions difficult to draw from the data; chronic pancreatitis with strictures or stones, pancreatic fistulae and disrupted pancreatic ducts are often reported in the same cohorts. Furthermore, many of these series report outcomes per patient rather than outcomes per procedure[71,76]. As patients may require more than one procedure to achieve technical success, this may bias the technical success rates positively, albeit while increasing the reported complication rate. However, the therapeutic success reported in these studies[29,71,72,76] is similar to that reported previously after ERCP based intervention[78]. Yet, for patients with chronic pancreatitis, surgery is frequently required and previous data suggests that it offers better outcomes than endoscopy for both pain and quality of life[79]. Randomized trials comparing ESCP and surgical intervention will need to be performed to resolve these issues.

Table 2 Summary of recently published reports of endoscopic ultrasound-guided pancreatic interventions including > 9 patients

Pancreatic	Procedures (*n*)	MPD access	Stent placement		Success	Procedure related complications		Notes
			RV	TM	Per procedure, *n* (%) [per patient, *n* (%)]	*n* (%)	Type	
Kinney *et al*[81] 2009	9	7/9 (78%)	4	-	4/9 (45%)	3/9 (33%)	Pancreatitis (1) Retroperitoneal and intraperitoneal air (1) Fever (1)	Retrospective All patients post Whipple procedure with endoscopic rendezvous attempted *via* the afferent limb Causes of failures: inability to access the MPD (2) and inability to traverse the pancreaticojejunal anastomosis with the guidewire (3) All patients with successful decompression had good short term clinical relief
Barklay *et al*[73]2010	21	18/21 (86%)	10[a]	-	10/21 (48%)	3/21 (14%)	Infection (1) Pancreatitis (1) Shaving of guidewire (1)	Retrospective Among 14 dilated MPDs and 7 normal calibre MPDs, the 3 failed pancreatograms occurred in patients with a normal calibre MPD Unable to pass wire to papilla in 8/12 patients: suboptimal angle (3), tight stricture (5) [a]Four patients successfully underwent rendezvous procedure, six patients successfully underwent repeat ERCP after methylene blue injection into MPD to aid identification of ampulla
Ergun *et al*[76] 2011	24 (20 pts)	20/20[b] (100%)	5	15	20/24 (83%) [18/20 (90%)]	2/24 (8%) [2/20 (10%)]	Bleeding (1) Perigastric collection (1)	Retrospective The reason for 24 procedures among 20 patients is unclear [b]Successful pancreatography reported in "all 20 patients"
Vila *et al*[52] 2012	19	NS	NS	NS	11/19 (60%)	5/19 (26%)	NS[c]	Retrospective case series pooling biliary and pancreatic intervention: 19 hospitals, 23 endoscopists, 106 biliary and 19 pancreatic interventions [c]Complication type per procedure is not specified. Of the 29 complications among the biliary and pancreatic interventions 5 were managed endoscopically, 3 with percutaneous intervention and 2 were managed surgically
Shah *et al*[47] 2012	30 (25 pts)	25/25[d] (100%)	9/16	10/14	19/30 (63%)[e] [19/22 (86%)[d]]	4/30 (13%)[e]	Pneumoperitoneum (1) Pancreatitis (3)	Retrospective [d]After pancreatography 3 patients were not felt to warrant intervention [e]30 therapeutic procedures were attempted (in 22 patients) due to significant crossover during intervention: 6 of 7 failed RV had attempted EUS guided antegrade therapy (5/6 successful); 2 of 3 failed antegrade EUS underwent attempted ERCP (double-balloon guided, 2/2 successful)
Kurahira *et al*[74] 2013	17 (14 pts)	17/17 (100%)	11	3 (4)[f]	15/17 (88%)	1/17 (6%)	Pssudocyst and aneurysm due to PD puncture (1)	Retrospective Two cases did not proceed after pancreatogram; complications during guidewire passage? [f]One patient had a temporary naso-pancreatic drain with subsequent stent insertions
Fujii *et al*[71] 2013	46 (43 pts)	45/46[g] (98%)	14	18	32/46[g] (70%) [32/43 (74%)]	16/46[g] (30%)	Abdominal Pain (13) Pancreatitis (1) Peri-panreatic abscess (1) Retained guidewire fragment (1)	Retrospective [g]For successful stent placement, three additional procedures were required in two patients

Superscripts refer to specific comments in the "Notes" column. ERCP: Endoscopic retrograde cholangio-pancreatography; EUS: Endoscopic ultrasound; MPD: Main pancreatic duct; Pts: Patients; RV: Rendezvous; TM: Transmural.

CONCLUSION

ESCP is an evolving technique facilitating biliary and pancreatic intervention where ERCP has failed. Although performed for almost two decades, the last five years have seen a substantial increase in the numbers of procedures

reported in the literature. These publications suggest that ESCP can provide high levels of technical success with acceptable complication rates. Where technical success is achieved, high rates of clinical success follow.

Despite the increase in reported experience with this technique, the cohorts described represent a heterogeneous group of conditions treated using a variety of procedures. Consequently, the optimal management of any specific condition is hard to define with certainty. Rendezvous procedures facilitated by ESCP have the highest reported success rates and lowest complication rates. In the appropriate circumstances, they may be considered as an alternative to precut sphincterotomy or PTC. Antegrade ESCP may be the therapeutic procedure of choice in very specific situations (*e.g.*, symptomatic stenosis of a pancreaticojejunal anastomosis in a patient with altered anatomy where the alternative intervention is surgery). In other clinical scenarios the role of ESCP is less certain.

Complications can be expected when performing these procedures. The majority can be managed conservatively. Where possible, using a trans-duodenal approach and covered metal stents may reduce the risks associated with biliary interventions. A high index of suspicion for complications should be maintained until the patient is clearly fit for discharge.

Although ESCP offers the potential for gastroenterologists to provide definitive care where ERCP has failed, and for patients to avoid surgery, enthusiasm for undertaking these procedures must be tempered with caution for two reasons. Firstly, the reported literature predominantly reflects the experience of a small group of highly skilled interventional endoscopists performing these novel procedures. Lower rates of success, and perhaps higher complication rates, can be expected in clinical practice. Formal training in these emerging techniques, coupled with an appropriate level of personal skill and experience, may be needed to achieve results approaching those reported by the procedural pioneers. To date, no societal guidelines specify the training criteria or experience required of endoscopists prior to undertaking these procedures. Secondly, perhaps with the exception of ESCP facilitated rendezvous procedures, trials evaluating the outcomes of the different subtypes of ESCP, and comparing ESCP to surgery, are required before it can be broadly recommended to patients. In these situations ESCP may be most appropriately considered only where ERCP has failed, after discussion with a multidisciplinary team and, where the technical expertise is available.

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REVIEW

Recto-sigmoid endoscopic-ultrasonography in the staging of deep infiltrating endometriosis

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Abstract

Recto-sigmoid endoscopic ultrasonography (RS-EUS) has first been used in the staging of pelvic deep infiltrating endometriosis in the early 1990's. Since then, although publications have been sparse, RS-EUS is routinely used for this indication in few centers. In this paper, we focus on technical aspects and operating method of rectal and sigmoid endo-sonography, and describe the most characteristic echographic presentations of endometriosis of the lower digestive tract. Through a literature review, results obtained with different types of endo-rectal probes, either flexible endoscopic, or blind rigid, are presented and compared with those of other close imaging techniques: magnetic resonance imaging and the more recent trans-vaginal sonography. As well as these two latter techniques, RS-EUS appears as an interesting method in the staging of pelvic deep infiltrating endometriosis particularly to evaluate rectal and sigmoid infiltrations. However, more prospective studies are required, to correctly define respective indications for each exam, in the light of recent advancements in treating this frequent disease.

Key words: Endometriosis; Rectum and sigmoid; Ultrasound; Endoscopic-ultrasonography; Surgical treatment; Magnetic resonance imaging

Core tip: Pelvic deep infiltrating endometriosis is a disabling disease of increasing rate. Today new medical and surgical therapies are proposed in the management of pain and infertility, and the choice of an optimal treatment strategy requires a precise anatomic evaluation. Several imaging techniques are available, either additive or competitive, in this staging. Rectosigmoid endoscopic-ultrasonography (RS-EUS), is routinely used in the field of gastroenterology, mostly for staging of rectal cancer. Few studies have demonstrated it could also be of interest to image endometriotic recto-sigmoid infiltrations. In this review, we tried to assess indications and results of RS-EUS, compared to those of magnetic resonance imaging and transvaginal sonography.

Roseau G. Recto-sigmoid endoscopic-ultrasonography in the staging of deep infiltrating endometriosis. *World J Gastrointest Endosc* 2014; 6(11): 525-533 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i11/525.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i11.525

INTRODUCTION

Pelvic deep infiltrating endometriosis affects 5% to 15% of women of reproductive age, and may hence impair quality of life of many young women suffering from pain and/or infertility[1,2]. When originating from recto-vaginal septum or retro-cervical areas, it has the potential to infiltrate the muscularis propria of rectum and sigmoid, characteristic locations of the so-called digestive tract endometriosis[3-5]. Diagnosis of this contingent infiltration is mandatory in order to correctly interpret clinical symptoms, either digestive or gynecologic, and to optimize treatment. Indeed management of pelvic deep infiltrating endometriosis relies on medical therapies or surgical interventions, and as far as recto-sigmoid locations are concerned, surgical laparoscopy is the reference

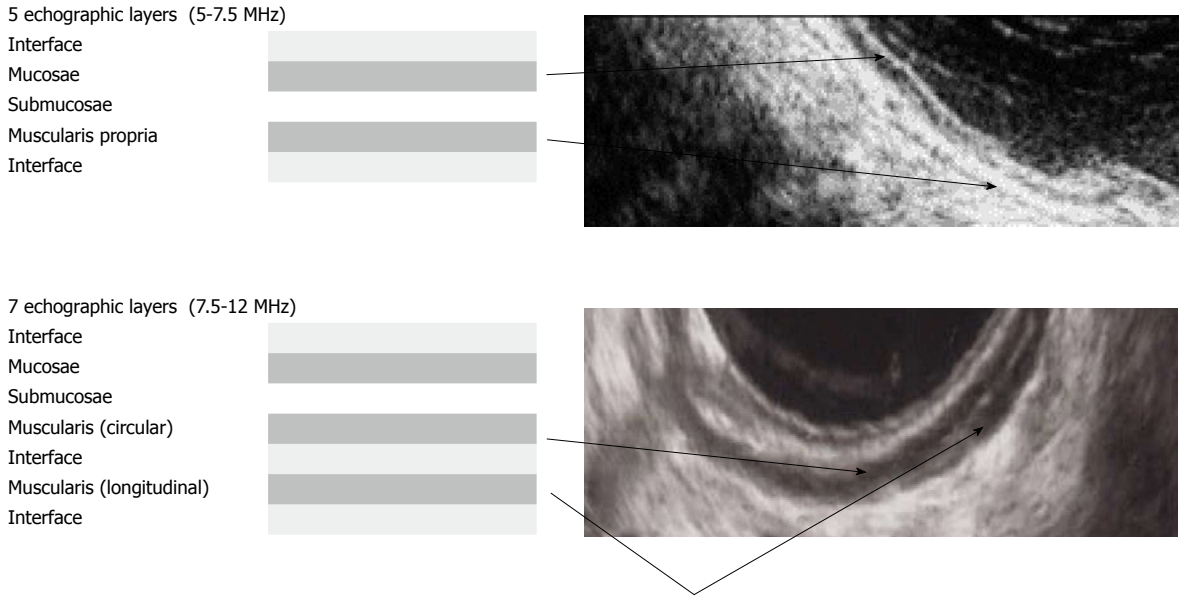

Figure 1 Digestive walls echoic stratifications depending on frequencies.

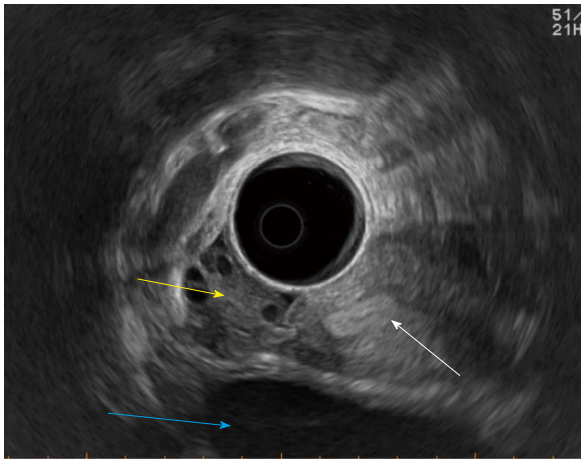

Figure 2 Normal peri-rectal anatomy. White arrow: Uterus; Yellow arrow: Right ovary; Blue arrow: Bladder.

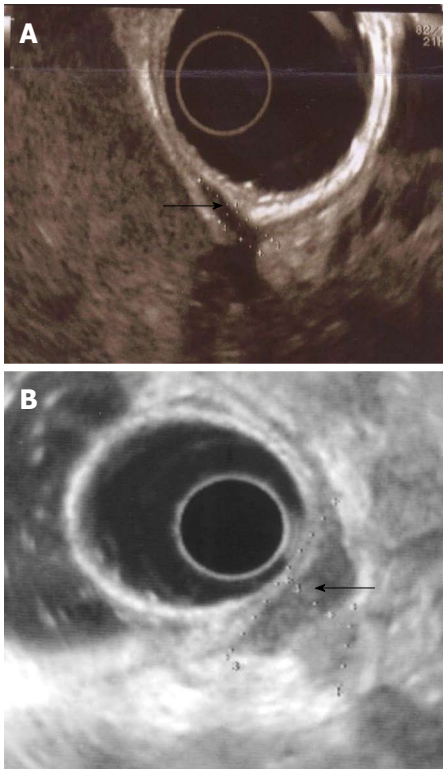

Figure 3 Different types of muscularis propria infiltration. A: Infiltration limited to external muscularis propria; B: Infiltration of the entire thickness of the muscularis propria.

technique for resection[6,7]. The recent trend is to prefer nodule excision, when feasible, than radical digestive resection[8,9], therefore it is of utmost importance to appreciate endometriotic rectal and sigmoid infiltration, in the pre-operative staging. Diagnosis of recto-sigmoid endometriosis definitely relies on imaging as clinical examination is not sufficient for the diagnosis of location of deeply infiltrating endometriosis[10]. Since the early 1980's different techniques, from barium enema to the most recent magnetic resonance imaging (MRI), have been proposed and evaluated to achieve diagnosis of endometriosis[3,11-13]. However these various imaging techniques have been used with variable results, equally to diagnose endometriosis and to evaluate its extension in pelvic locations such as uterosacral ligaments (USL), recto-sigmoid, recto-vaginal septum and bladder. Today, three endocavitary ultrasonic exams, transvaginal sonography (TVS), blind endo-rectal sonography (ERS), and recto-sigmoid endoscopic ultrasonography (RS-EUS), are also available[14-16], the latter, although slowly developing, appears as an interesting technique. In this review we will first consider technical aspects and operative method of RS-EUS, and describe echographic presentations of recto-

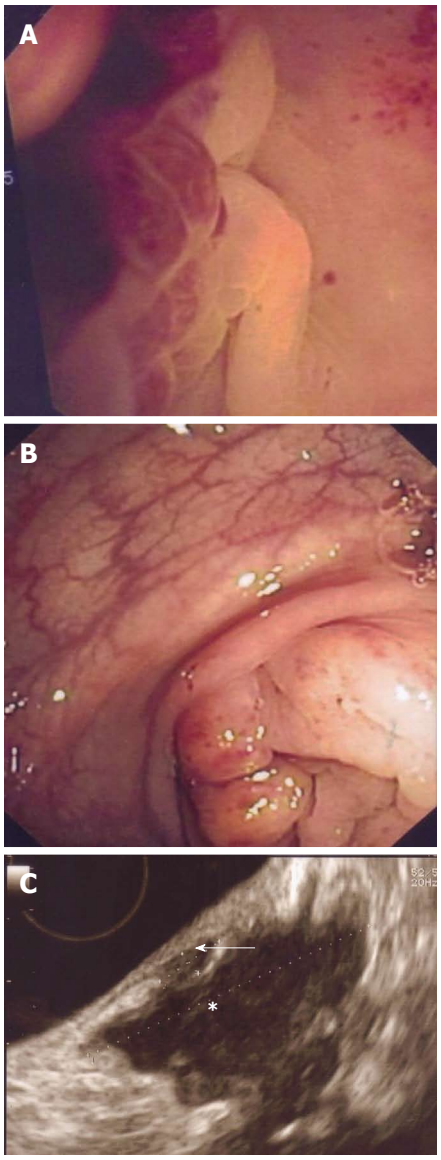

Figure 4 Endoscopic and echographic presentations of recto-sigmoid endometriosis. A: Mucosae infiltration; B: Sigmoïd stenosis; C: Sub-mucosae (white arrow) and muscularis (white star) infiltrations.

sigmoid, either normal or infiltrated by endometriosis. Then, performances of recent imaging in the staging of deep infiltrating endometriosis will be discussed, with a special focus on results of RS-EUS in staging of recto-sigmoid endometriosis infiltration.

RS-EUS, TECHNICAL CONSIDERATIONS AND ECHOGRAPHIC PRESENTATION OF NORMAL RECTO-SIGMOID PARIETAL WALLS AND SURROUNDINGS

Initially proposed in the early 1980's mostly for rectal cancer staging[17,18], RS-EUS was first described in the evaluation of recto-sigmoid endometriosis in 1993[19]. In this early work, a radial RS-EUS (GF UM2), from Olympus was used, allowing circular images of 360°. This device was a flexible optical scope equipped with an echographic probe of 7.5 MHz frequency. Ever since then, many other radial scopes with a mechanical transducer (*GF UM3, GF UM20,* and *GF UM 160*) have been used to stage patients with pelvic deep infiltrating endometriosis. These scopes have diameters and frequencies respectively varying from 10.4 to 11.5 mm and 5 to 20 MHz. In 2008 the electronic probe (GF-UM160, 13.8 mm diameter and variable frequencies from 5 to 10 MHz) became available. To date, this video-echoendoscope is used connected to alpha 5 or alpha 10 dedicated central ultrasound unit device allowing doppler function. Other similar devices from Pentax (*reference EG 3630 UR*) and Fujinon (*reference EG-530 UR with SU-7000 ultrasound system*) have also been used with similar efficiency. On the other hand, the use of linear scopes, probably less suitable in this indication has never been reported. RS-EUS is usually performed without the recourse to general anesthesia, after one or two rectal Normacol^{R} enemas, the patient lying on the lithotomy position. Progression of the endoscope is initiated under endoscopic and ultrasonic control up to the recto-sigmoid junction, and above, in the distal sigmoid when possible. Most part of the endoscopic exploration is done while progressing (looking for stenosis, extrinsic compressions, relief and mucosal coloration abnormalities …), while ultrasonic exam is performed when slowly withdrawing the probe[20]. Rectal and sigmoid parietal walls are explored, and semiology interpreted according to the well-known 5 or 7 layers description of the digestive tract (Figure 1), while anatomical structures around the digestive tract are simultaneously imaged (Figure 2).

ECHOGRAPHIC PRESENTATIONS OF RECTO-SIGMOID ENDOMETRIOSIS AND OF SOME OF THE CLOSE PELVIC LOCATIONS

Endometriotic infiltration of the muscularis-propria defines endometriosis of the digestive tract[21]. Rectum and sigmoid are the most frequent locations representing 90% of cases[3,4], and infiltration is imaged, by endorectal ultrasound using 5 or 7 MHz frequencies, as a hypoechoic thickening of the muscularis-propria corresponding to the fourth layer, from superficial to deep part of the parietal wall (Figure 3). Instead with 10 to 12 MHz frequencies, lesions infiltrating the entire muscularis-propria or solely the external longitudinal layer can be differenciated. Depending on their origin (torus uterinus or USL), these thickenings respectively stand on the median line or on the lateral surfaces of the rectum and/or sigmoid. In 15% of cases separated locations can also be found in the sigmoid[3,5].

In all cases, measurements should be imperatively performed either in depth, width, and height. Complete evaluation by using figures in degrees of the circumference, and specification of distance in centimeters, be-

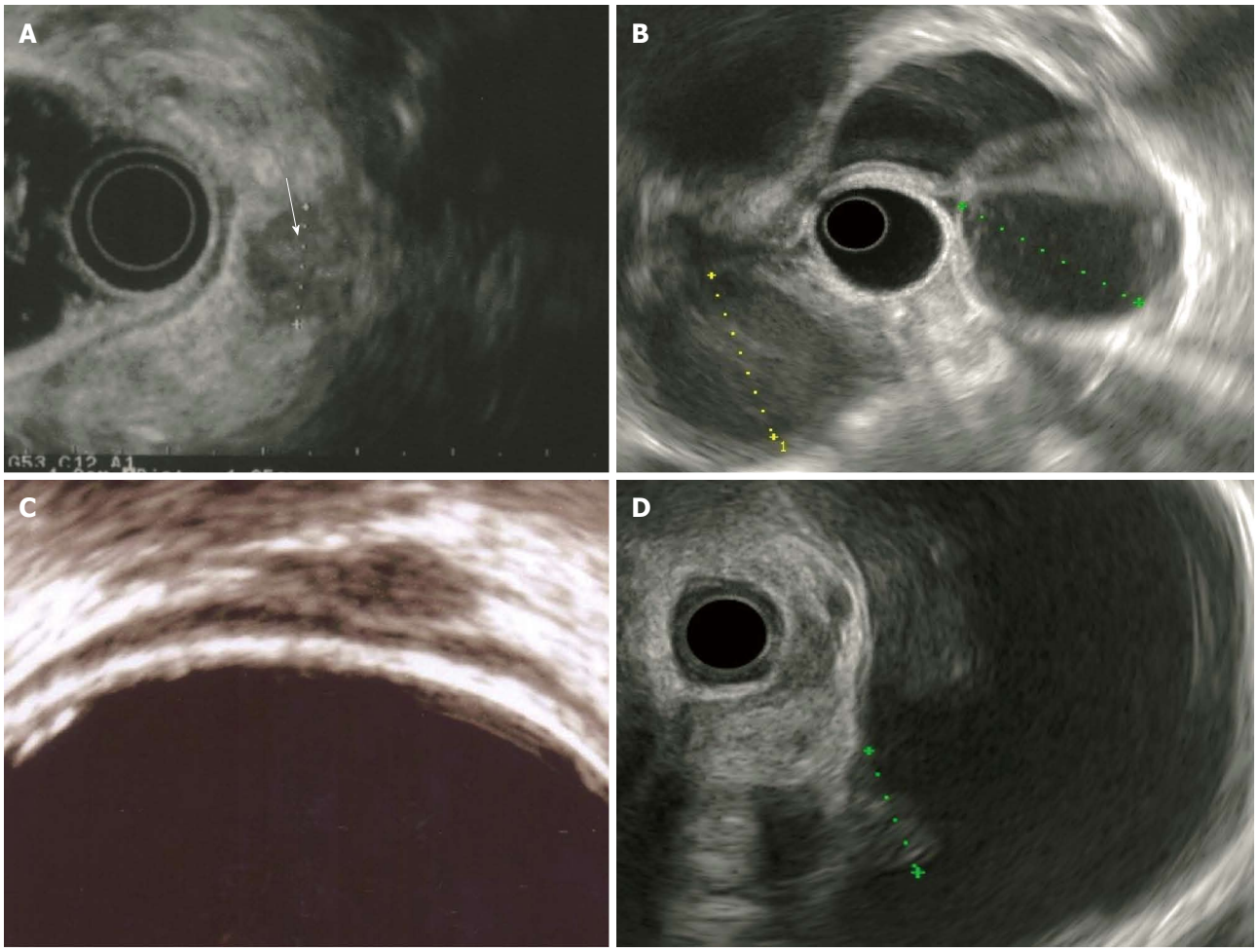

Figure 5 Other pelvic endometriosis locations. A: Infiltrated Torus; B: Bilateral Ovarian endometriomas; C: Infiltrated utero-sacral ligament; D: Bladder nodule.

Table 1 Main "exclusive" blind endo-rectal or endoscopic ultrasonography[1] in deep infiltrating endometriosis

Author	Ref.	Year	No.	Type	se%	sp%	ppv%	npv%
Roseau[1]	[19]	1993	(11)	Descriptive rectal endometriosis				
Hauge	[27]	1993	(1)	Descriptive, anal endometriosis				
Ohba	[26]	1996	64	Descriptive, correlation thickness USL and clinical symptoms				
Chapron[1]	[29]	1998	38 (17)	R preliminary results		Diagnosis accuracy: 100%		
Fedele	[28]	1998	140 (24)	R	97	96		
Roseau[1]	[16]	2000	46 (25)	R	100	100		
Doniec	[30]	2003	65 (32)	R	97	97		
Abrao[1]	[31]	2004	32 (6)	R	100	67		
Delpy[1]	[32]	2005	30 (17)	P	92	66	64	92
Bahr	[33]	2006	37 (8)	R	87.5	97	87.5	97
Roman[1]	[34]	2007	(16)	Kappa coeff: 0.22; limited accuracy to predict layer involvement				
Griffiths	[14]	2008	32	Likekihood ratio + : 10.89/-: 0.24; good results for recto-vaginal septum				
Mezzi[1]	[35]	2011	68 (34)					
Ferrari[1]	[36]	2012	(26)	Diagnosis accuracy: 100% with elastometry				
Rossi[1]	[22]	2013	(38)	R	89	26	55	71

[1]Main "exclusive" blind endo-rectal or endoscopic ultrasonography. ( ): Patients with digestive infiltration/type; R: Retrospective; P: Prospective; se: Sensitivity; sp: Specificity; ppv: Positive predictive value; npv: Negative predictive value; USL: Utero-sacral ligament.

tween the lowest part of the digestive infiltration and the pubo-rectal muscle or the anal verge, provides precious informations in the pre-operative staging. In patients with advanced disease, superficial irregularities and abnormal mucosal coloration or stenosis, can be encountered endoscopically, corresponding to entire muscularis-propria or even sub-mucosae infiltration. The latter can be certified either on endoscopy or ultrasonography when significant,

Table 2 Evaluation of magnetic resonance imaging in staging deep infiltrating endometriosis

Anatomical location	se%	sp%	acc%	ppv%	npv%
Global	90.3	91	90.8	92.3	89
USL	76	83.3	80.5	74	84.7
Vagina	76	95.4	93.3	67	97
Septum	80	97.8	96.9	67	98.7
Recto-sigmoid	88	97.8	94.9	95	95
Bladder	88	98.9	97.9	88	98

Bazot *et al*[13], 2004: 195 patients treated by laparoscopy: *n* = 136 or laparotomy: *n* = 59; all specimens sent for histological examination as the gold standard. se: Sensitivity; sp: Specificity; ppv: Predictive positive value; npv: Negative predictive value; acc: Accuracy rate.

or only suspected in other cases (Figure 4). Indeed, to date, no imaging technique has been demonstrated as a reference in diagnosing mild sub-mucosae infiltration[22,23]. Beside, other locations of pelvic deep infiltrating endometriosis can also be imaged with RS-EUS, either torus uterinus, USL and bladder (Figure 5). Ovarian endometriomas whatever their size are characterized by their "ground glass" echogenicity[24].

RESULTS OF IMAGING (MRI AND ULTRASOUND), IN THE STAGING OF DEEP INFILTRATING ENDOMETRIOSIS; WHAT SHOULD BE THE PLACE OF RS-EUS?

For surgeons and gynecologists specialized in deep pelvic endometriosis, treatment decisions rely on several factors depending on the patient (age, intensity of the symptoms, and response to previous treatments), and the disease (loco-regional extension). Ureter dilatation and the risk of renal insufficiency must always be kept in mind and systematically searched on imaging[25]. The other major question raised, concerns diagnosis of recto-sigmoid infiltration, either suspected on clinical signs (dyschesia, cyclic pains, transit time variations, or hematochezia), or systematically screened for, prior to surgical intervention. From a literature review using the key-words below (rectosigmoid endometriosis and ultrasound, endosonography, endoscopic ultrasonography, transvaginal sonography, and MRI) we tracked all "exclusive" RS-EUS and rectal endo-sonography studies, and searched for series, especially comparative with ultrasound, evaluating MRI in the loco-regional extension of pelvic endometriosis.

Exclusive endo-rectal ultrasound studies

There are only few exclusive studies evaluating the use of endo-rectal ultrasound in diagnosis and staging of recto-sigmoid endometriosis[14,16,19,27-36]; they are presented in Table 1. Almost all are retrospective studies, and they have the limitation to be widely disparate in terms of purposes studied, and technical devices tested. Ohba *et al*[26] are the only authors whose report had the aim to demonstrate the usefulness of endo-rectal ultrasound in imaging USL. In this early paper, the type of probe used was a blind poly-plane probe (two dimensional mechanical sector probe); USL's description was performed in patients with or without endometriosis infiltration of these ligaments. Comparisons showed that patients with endometriosis had thickened and irregular ligaments, with correlation between the thickness and the intensity of pain. However, in no other study, whatever the probe used, normal USL has been correctly described. Actually, and this is consistent with most author's descriptions, endo-rectal ultrasound examination can localize USL clearly, only when it is already infiltrated by endometriosis.

Globally, when trying to answer to the question of the presence (or not) of endometriotic recto-sigmoid parietal infiltration, short series available, most of them published between 1998 and 2008[14,22,28-34], show close sensitivities and negative predictive values, as well as with blind and endoscopic probes. Comparison of Delpy and Bahr's studies, clearly illustrates this conclusion[32,33]. Sensitivity and specificity range respectively from 87% to 100% and 66% to 100% and the superiority of RS-EUS over blind rigid probes does not appear; this could be explained by the limited number of patients included, and the low prevalence of isolated upper sigmoid lesions already mentioned above[3]. However, when looking at the 9 over 15 studies, in which the ultrasound device used was RS-EUS [Table 1, authors marked with (1)]; diagnosis accuracy may reach 100%, and in our own study published in 2000, we found the same high values of sensitivity and specificity. Furthermore, in their prospective study, Delpy *et al*[32] have demonstrated high sensitivity (92%) and negative predictive values (92%) with RS-EUS.

In the two studies from Rossi *et al*[22] and Roman *et al*[34], the aim was to evaluate precise parietal layer involvement. Compared to performances in the positive diagnosis of recto-sigmoid endometriosis, endo-rectal ultrasound is not as much demonstrative in this appreciation. Such results rely on incorrect sub-mucosal involvement' s evaluation, and it is interesting to notice that the same limitation has also been recently reported by Busard *et al*[23] with MRI. As for the interest of fine needle aspiration endoscopic ultra-sonography (FNA/EUS), it does not really concern the evaluation of parietal wall by endometriosis. Only mentioned in few papers, it can benefit to patients with para-rectal masses, the differential diagnosis of which can be resolved by puncturing under ultrasound control[37-39].

Comparative studies between endorectal ultrasound and other imaging techniques

Other imaging techniques than endo-rectal ultrasound are also used to diagnose and stage pelvic deep infiltrating endometriosis. MRI has first been proposed in the late 1990's[40-43]; both technical improvement and learning curves, have led to good results published first by Bazot *et al*[13] in a prospective serie. In this work presented on Table 2, 195 patients were included, who all had surgical treatment (laparoscopy: *n* = 136, laparotomy: *n* = 59)

Table 3 Comparative studies magnetic resonance imaging *vs* recto-sigmoid endoscopic ultrasonography in staging deep infiltrating endometriosis

Author	Ref.	Year	No.	Type	se%		sp%		ppv%		npv%	
					MRI	RS-EUS	MRI	RS-EUS	MRI	RS-EUS	MRI	RS-EUS
Dumontier	[47]	2000	48 (16)	R	75	100	100	100				
Camagna	[48]	2004	50 (19)	R	53	100	82	71	69	81	19	100
Thomassin	[49]	2004	(27)	P	92	100			89	100		
Chapron	[50]	2004	81 (17)	R	76.5	97	98	89.4	96	87	85	98
Bazot	[51]	2007	88 (60)	P	88.3	90	92.8	89.3	96.4	94.7	78.8	80.6
Benbara	[52]	2008	50 (40)	R	55	100			Post operative follow up			
Gauche-cazalis	[53]	2012	25 (19)	R	89	94	50	66.7	MRI contributive for torus, USL and bladder			

( ): Number with digestive infiltration; R: Retrospective; P: Prospective; se: Sensitivity; sp: Specificity; ppv: Predictive positive value; npv: Negative predictive value; MRI: Magnetic resonance imaging; RS-EUS: Recto-sigmoid endoscopic ultrasonography; USL: Utero-sacral ligament.

Table 4 Comparative studies trans-vaginal sonography *vs* recto-sigmoid endoscopic ultrasonography in staging deep infiltrating endometriosis

Author	Ref.	Year	No.	Type	se%		sp%		ppv%		npv%	
					TVS	RS-EUS	TVS	RS-EUS	TVS	RS-EUS	TVS	RS-EUS
Bazot	[54]	2003	30	P	95	82	100	88	100	95	89	84
Bazot	[56]	2003	81	P	92	88.9	100	92.6	89	100	87	80.6
Piketti	[57]	2009	134	P	90.7	96	96	100	100	96	88.9	95.2
Gauche-cazalis	[53]	2011	25	R	73.7	94.7	66.7	66.7	RS-EUS : Appropriate for rectum and recto-vaginal septum TVS: Good for ovarian endometriomas			

( ): Number of patients with digestive infiltration; R: Retrospective; P: Prospective; se: Sensitivity; sp: Specificity; ppv: Positive predictive value; npv: Negative predictive value; RS-EUS: Recto-sigmoid endoscopic ultrasonography; TVS: Trans-vaginal sonography.

and histological examination as a gold standard. MRI performances were evaluated for the main locations of pelvic deep infiltrating endometriosis, and results were given both globally, and for each of them. Since then, other studies evaluating MRI with a similar methodology have been published with same promising results[44-46]. As for comparative studies, those concerning RS-EUS and MRI, have been published principally between 2000 and 2010[47-53], whereas the first prospective one comparing performances of RS-EUS and TVS was published in 2003[54], soon followed by other papers[55-58]. Comparisons often rely on both recto-sigmoid parietal involvement, and also on other main locations of deep pelvic endometriosis (*i.e.*, Bladder, Recto-vaginal septum, Torus, USL), and on ovaries. Yet it is difficult to correctly appreciate specific results unless working on selected papers where distinction of each location would be correctly performed. We have reported these studies in the Tables 3 and 4. Comparisons of MRI and RS-EUS show improvements of MRI's results with time, and for RS-EUS fair results for specificity (66.7%-100%) and good ones both for sensitivity (90%-100%), predictive positive value (81%-100%), and negative predictive value (80.6%-100%). Two studies, from Thomassin *et al*[49] and Bazot *et al*[51], are prospective; the former shows better sensitivity and positive predictive values for RS-EUS whereas for Bazot *et al*[51], the superiority of RS-EUS over MRI only concerns sensitivity and negative predictive value. For specificity and positive predictive value, MRI has a slight advantage although non statistically significant. As for the studies comparing RS-EUS and TVS, 3 of them are prospective; the first one from Bazot *et al*[54], already mentioned, favors TVS, and the main ones from the same author[56], and Piketti *et al*[57] curiously demonstrates strictly inverse results with only slight differences. Both authors conclude than TVS is the perfect first line exam, and that RS-EUS may be useful as a second exam to certify the absence of parietal involvement if TVS is negative. It may also be used to provide an accurate description of parietal wall infiltration when surgery is mandatory, or as a baseline measurement for patients with continuous low doses oral contraceptive treatment[36]. In the work of Huang (meta-analysis on ultrasound evaluating RS-EUS, blind ERS and TVS for deep infiltrating endometriosis, all locations combined), ERS had the highest performances (sensitivity and specificity of 92% and 98%), and areas under the curve of RS-EUS was 94%, and that of TVUS was 92%[58].

As MRI, RS-EUS and TVS are complementary imaging exams, it is important to determine in which locations

Table 5 Retrospective comparative study between trans-vaginal sonography, recto-sigmoid endoscopic ultrasonography, and magnetic resonance imaging for diagnosis of main locations of deep pelvic endometriosis

	OV			Torus			USL			RVS			RSJ			Bladder		
	TVS	RS-EUS	MRI	TVS	RS-EUS	MRI	TVS	RS-EUS	MRI	TVS	RS-EUS	MRI	TVS	RS-EUS	MRI	TVS	RS-EUS	MRI
se (%)	88	80	87	57	76	76	63	37	69	63	89	47	73	95	89	16	16	33
sp (%)	71	81	71	100	100	100	82	100	82	100	67	100	66	66	50	100	100	89

Gauche Cazalis *et al*[53] 2012: 25 patients included. OV: Ovary; USL: Uterosacral ligament; RVS: Rectovaginal septum; RSJ: Rectosigmoïd junction; se: Sensitivity; sp: Specificity are expressed in %.

each has the best diagnosis performances. This has been studied by Gauche Cazalis *et al*[53] in a retrospective manner; results are presented in Table 5. In this work with 25 patients included, authors conclude that TVS is accurate for endometriomas, MRI for torus, USL, and small bladder lesions, while RS-EUS is particularly appropriate for recto-vaginal septum and recto-sigmoid parietal wall's involvement[53]. Unfortunately this is a small retrospective study, and such results only could be confirmed by using prospectively such an "exhaustive staging methodology" through multi-centric studies.

CONCLUSION

RS-EUS is a promising tool for the diagnosis of digestive endometriosis. It has the advantage to combine endoscopic and ultrasonic evaluation of the rectum and the distal part of sigmoid where most cases of endometriosis of the digestive tract are localized. It allows a more complete exam than blind rigid rectal probe which can be deficient in diagnosing sigmoid lesions. Compare to other imaging exams appropriate for staging of pelvic deep infiltrating endometriosis, RS-EUS, is prone to diagnose parietal wall and recto-vaginal septum infiltrations, whereas MRI and TVS seem more appropriate in diagnosing ovarian endometriomas, and torus, USL or bladder infiltrations. However, precise performances for these three complementary explorations should be studied in prospective works, in order to exactly define which patients should really benefit from RS-EUS.

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MINIREVIEWS

Nodular lymphoid hyperplasia in the gastrointestinal tract in adult patients: A review

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Abstract

Nodular lymphoid hyperplasia of the gastrointestinal tract is characterized by the presence of multiple small nodules, normally between between 2 and 10 mm in diameter, distributed along the small intestine (more often), stomach, large intestine, or rectum. The pathogenesis is largely unknown. It can occur in all age groups, but primarily in children and can affect adults with or without immunodeficiency. Some patients have an associated disease, namely, common variable immunodeficiency, selective IgA deficiency, *Giardia* infection, or, more rarely, human immunodeficiency virus infection, celiac disease, or *Helicobacter pylori* infection. Nodular lymphoid hyperplasia generally presents as an asymptomatic disease, but it may cause gastrointestinal symptoms like abdominal pain, chronic diarrhea, bleeding or intestinal obstruction. A diagnosis is made at endoscopy or contrast barium studies and should be confirmed by histology. Its histological characteristics include markedly hyperplasic, mitotically active germinal centers and well-defined lymphocyte mantles found in the lamina propria and/or in the superficial submucosa, distributed in a diffuse or focal form. Treatment is directed towards associated conditions because the disorder itself generally requires no intervention. Nodular lymphoid hyperplasia is a risk factor for both intestinal and, very rarely, extraintestinal lymphoma. Some authors recommend surveillance, however, the duration and intervals are undefined.

Key words: Nodular lymphoid hyperplasia; Gastrointestinal tract; Adults; Endoscopy; Lymphoma

Core tip: Published literature about nodular lymphoid hyperplasia includes mainly case reports and small series of patients, there are no reviews concerning this topic. The aim of this large and comprehensive review is to provide current knowledge regarding nodular lymphoid hyperplasia, which may be of great help to clinicians in their daily practice.

Albuquerque A. Nodular lymphoid hyperplasia in the gastrointestinal tract in adult patients: A review. *World J Gastrointest Endosc* 2014; 6(11): 534-540 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i11/534.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i11.534

DEFINITION

Nodular lymphoid hyperplasia (NLH) of the gastrointestinal tract is characterized by the presence of multiple small nodules, between 2 and 10 mm in diameter. Although it may be detected in the stomach, large intestine or rectum[1], it is more often distributed in the small intestine. Histologically, NLH is defined by markedly hyperplastic, mitotically active germinal centers, and well-defined lymphocyte mantles found in the lamina propria and/or in the superficial submucosa[2].

EPIDEMIOLOGY

The incidence is unknown, nevertheless, NLH is considered to be a rare condition in adults[3-6] and published

literature includes mainly case reports and small series of patients; whether this relates to endoscopy underreporting or to the true rarity of the condition in adults is unclear[7].

NLH occurs in all age groups[3,8], but primarily in children under ten years of age, when general lymphatic hyperplasia is common[9]. Reported gender distribution of this condition is conflicting[3,10].

CLASSIFICATION

NLH has been divided into diffuse nodular lymphoid hyperplasia and focal forms, mainly involving the terminal ileum, rectum, or other sites in the gastrointestinal tract[1,2,11].

Pediatric NLH is generally restricted to the rectum, colon, and terminal ileum, has a benign course, and usually regresses spontaneously[3,12-14]. It has been linked to refractory constipation[15], viral infection, and food allergies[12,13]; however it can be observed in healthy children[16]. In adults, the prognosis is much less certain, and NLH can be divided into those with or without immunodeficiency[17], but, normally, it is associated with immunodeficiency and *Giardia* infection[18].

PATHOGENESIS

The pathogenesis of NLH is largely unknown, but there are some theories that explain this condition and vary according to the presence or absence of associated immunodeficiency.

In immunodeficiency states, in order to compensate for functionally inadequate intestinal lymphoid tissue, NLH may result from an accumulation of plasma-cell precursors due to a maturational defect in the development of B-lymphocytes[11,19].

NLH in the absence of immunodeficiency disorders may be related to immune stimulation of the gut lymphoid tissue. A frequently proposed hypothesis implicates an intestinal antigenic trigger, possibly infectious, that leads to repetitive stimulation and eventual hyperplasia of lymphoid follicles. The frequent association between *Giardia* infection and NLH suggests this, even in the absence of humoral immunodeficiency[8].

Chiaramonte *et al*[20] hypothesized that NLH could be a transitional stage in the development of a malignant lesion, or possibly an early lymphomatous lesion. NLH is a risk factor for intestinal lymphoma and there are studies suggesting that lymphoid-associated colorectal mucosa might be the origin of many non-protruding adenomas and consequently of non-protruding early colorectal carcinomas[21].

ASSOCIATED DISEASES

NLH has been reported in immunocompromised and immunocompetent adult patients.

Approximately 20% of adults with common variable immunodeficiency disease (CVID) are found to have NLH[6,19,22-31]. NLH is also associated with IgA deficiency[22,32-35] and has also been reported in patients with human immunodeficiency virus (HIV) infection[36].

CVID is characterized by the significantly reduced levels of IgG, IgA, and/or IgM, impaired antibody response, with the exclusion of other causes of hypogammaglobulinemia. Patients typically present with recurrent bacterial infections of the upper and lower respiratory tracts, autoimmune disease, granulomatous/lymphoid infiltrative disease, and increased incidence of malignancy. NLH in CVID patients is usually more generalized, involving the proximal small intestine, in addition to the distal ileum and proximal colon[22].

Selective IgA deficiency is the most common primary immunodeficiency, estimated at 1 in 300 to 700 in Caucasians, (IgA < 7 mg/dL with normal or increased levels of other immunoglobulins). The majority of patients are asymptomatic, although the absence of IgA has been associated with recurrent upper respiratory infections (frequently in those with concomitant IgG2 subclass deficiency), autoimmune disorders, allergic diseases and gastrointestinal diseases, namely NLH[37].

Giardia lamblia infection can be associated with NLH[3,10], more commonly in patients with immunodeficiency[38-40], but also in patients without immunodeficiency[4,41]. The association between NLH, hypogammaglobulinemia, and *Giardia lamblia* infection is known as Herman's syndrome[11].

The link between NLH and celiac disease seems to be rare[3,32]. It is important to underline that CVID patients may present small-bowel pathology similar to classic celiac sprue, known as "pseudo-celiac" pattern, with short villi, crypt hyperplasia, intraepithelial lymphocytosis, and, in some cases, an increase in apoptotic bodies in crypt epithelial cells. The diagnosis of CVID should be suspected when the number of plasma cells are reduced or absent in the lamina propria, and patients do not produce antibodies to tissue transglutaminase, endomysium, or gliadin. CVID patients typically do not respond to gluten withdrawal and do not express the genes associated with celiac disease, HLA-DQ2 and HLA-DQ8[3,37].

Helicobacter pylori (*H. pylori*) infection has also been implicated in NLH[18,42]. Khuroo *et al*[18] reported a large cohort of patients (40 patients) with NLH, etiologically related to *H. pylori* infection. Patients with eradicated *H. pylori* showed significant clinical response and regression/resolution of the lesions, in contrast to patients with persistent *H. pylori* infection. The location, in these cases, was limited to the postbulbar duodenum (second and third part) and to the duodenojejunal junction. None of the patients included in this study had an immunodeficiency or giardiasis. NLH was attributed to immune stimulation by prolonged and heavy *H. pylori* infection.

Familial adenomatous polyposis and Gardner's syndrome[43-46] was also linked to NLH mainly involving the terminal ileum.

There are also several case reports where no relation

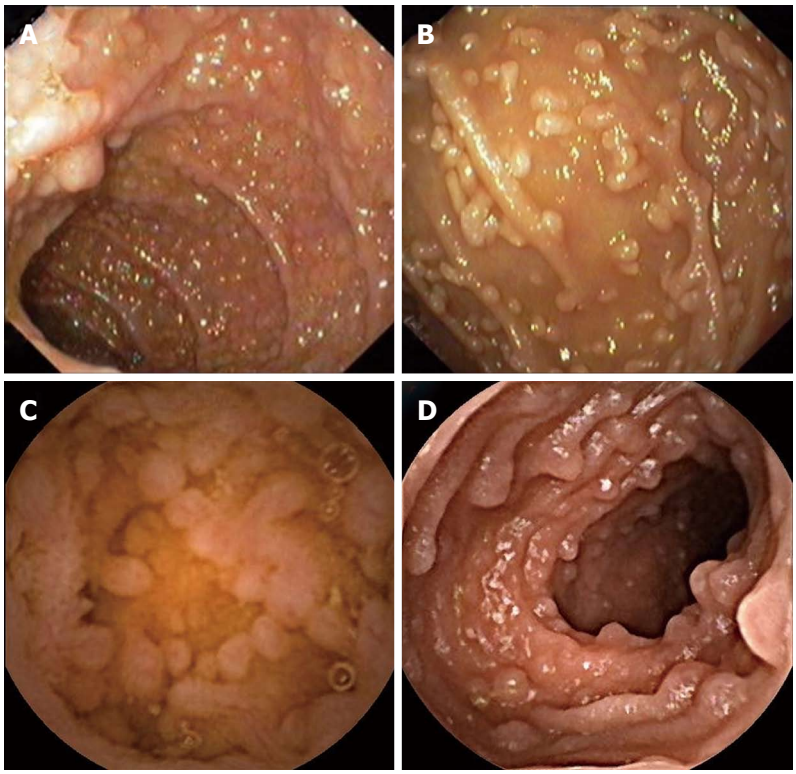

Figure 1 Endoscopic appearance of nodular lymphoid hyperplasia. A: Upper endoscopy revealing a nodular lymphoid hyperplasia of the duodenal bulb in a patient with common variable immunodeficiency; B: Upper endoscopy showing nodular lymphoid hyperplasia of the second part of the duodenum in a patient with selective IgA deficiency; C: Small bowel capsule endoscopy revealing a nodular lymphoid hyperplasia of the jejunum in a patient selective IgA deficiency; D: Small bowel capsule endoscopy revealing a nodular lymphoid hyperplasia of the terminal ileum in a patient with common variable immunodeficiency.

with any of the diseases described above was found[2,47,48].

CLINICAL MANIFESTATIONS

NLH can present as an asymptomatic disease (in the majority of the patients) or with gastrointestinal symptoms like abdominal pain, chronic diarrhea, bleeding, intussusception or intestinal obstruction[5,49].

Massive hyperplasia that can result in intestinal obstruction and intussusception is very rare and mainly described in children[9,50]. *H. pylori*-induced gastric lymphonodular hyperplasia, causing gastric outlet obstruction, was reported in one case. Anti-*H. pylori* therapy resulted in eradication and the resolution of signs and symptoms of gastric outlet obstruction[42].

Colón *et al*[12] published a retrospective analysis including 147 children with NLH and 32% of the cases had bright red blood emission per rectum. In adult patients, NLH uncommonly causes gastrointestinal bleeding and may manifest as massive obscure[51,52], recurrent[53,54] or rectal bleeding[55].

DIAGNOSIS

The diagnosis of NLH is established by endoscopy or contrast barium studies and confirmed histologically. There are several other entities that can mimic NLH, and since misdiagnosis could lead to overtreatment of a benign condition, histopathology is fundamental for the diagnosis[5].

Endoscopic features of NLH include nodules ranging in size from 2 mm to 10 mm, but normally not exceeding 5 mm in diameter (Figure 1A and B). These nodules may present in the stomach, small intestine (terminal ileum is the most common), and colon/rectum. Colonic lymphoid nodules may appear as red macules, as a circumferential target lesions (halo sign), or as raised papules[56,57]. When the large intestine is involved, the rectum is most commonly implicated[58,59]. In NLH involving the colon, the endoscopic appearance can be strikingly similar to polyposis syndromes, including familial adenomatous polyposis, multiple lymphomatous polyposis, juvenile or hamartomatous, polyposis and serrated polyposis syndrome, among others[58]. There is a case report of an adult immunocompetent patient with NLH in a defunctionalized colon, following ileostomy performed because of localized regional ileitis[60]. This had only been previously described in children[61].

NLH is diagnosed when the following histological criteria (Figure 2) are observed: hyperplasic lymphoid follicles, mitotically active germinal centers with well-defined lymphocytes mantles, and lymphoid follicles localized in the mucosa and/or submucosa[2].

In NLH involving the small bowel, small bowel barium swallow and, mainly, capsule endoscopy are important for the diagnosis, to exclude complications (like lymphoma), and to determine disease extension in the small bowel (Figure 1C and D).

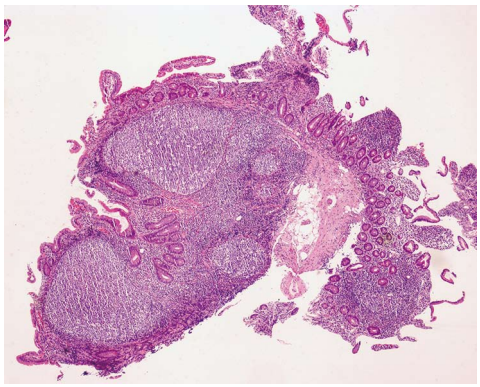

Figure 2 Duodenal biopsies stained with haematoxylin-eosin (× 40), with hyperplasic lymphoid follicles, suggesting nodular lymphoid hyperplasia.

Small bowel barium swallow can be diagnostic by revealing multiple, round-shaped nodular filling defects in the small bowel segments[23].

In the presence of NLH, immunodeficiency (CVID, selective IgA deficiency and HIV infection), giardiasis, celiac disease, and *H. pylori* infection should be suspected.

In general, colonic NLH is considered of no clinical significance[7,55].

NLH can resemble both clinically and histologically malignant lymphoma[62]. It can be distinguished by the polymorphic nature of the infiltrate, the absence of significant cytologic atypia, and the presence of reactive follicles within the lesion, and by use of immunohistochemical or molecular analysis[1]. Among primary intestinal lymphomas, mantle cell lymphoma is most frequently represented by multiple polypoid lesions[63]; however, less frequently, extranodal marginal zone lymphoma or mucosa-associated lymphoid tissue-MALT[64], and follicular lymphoma[65] also show multiple lymphomatous polyposis.

Gastric involvement is rare[1]. The differential diagnosis of gastric lymphoid lesions includes reactive processes and malignant lymphoma. In such cases, it is important to rule out extranodal marginal zone lymphoma[66]. Some gastric lesions are associated with chronic peptic ulcers, but ulceration is absent or insignificant in focal lesions located in the intestine[1].

TREATMENT AND FOLLOW-UP

Treatment is directed to associated conditions because the disorder itself generally requires no intervention[5].

In both immunodeficient and immunocompetent patients with NLH, the eradication of *Giardia* often causes the intestinal symptoms to disappear[11]; nevertheless, in most reported cases, successful treatment of the infection did not lead to a regression in the number or size of the lymphoid nodules[24,67], although this also has been described[17].

NLH is a risk factor for both intestinal and, very rarely, extraintestinal lymphoma, previously reported in patients with and without immunodeficiency[2,20,68-77]. The link between extraintestinal lymphoma[4,47,78] and NLH is uncommon. Jonsson *et al*[78] reported a case of extraintestinal lymphoma associated with NLH, in which, hyperplastic tissue completely disappeared after chemotherapy with remission of the lymphoma and reappearance at relapse.

A study from Japan and Sweden also suggests an association between colonic lymphoid nodules and non-protruding colorectal neoplasia, adenomas, and early carcinomas[21].

Considering the risk of malignant transformation, surveillance capsule endoscopies and small bowel series are recommended by some authors in small bowel NLH[59] however, the duration and intervals of such surveillance are undefined; biopsy of enlarging lymphoid nodules should be performed to exclude lymphomatous transformation[32].

PERSPECTIVE

There are several missing pieces in the NLH puzzle, including: epidemiological data (incidence, prevalence, gender distribution), pathogenesis, and clarification about the role that other endoscopic or non-endoscopic procedures have in NLH evaluation, such as, enteroscopy. Most importantly an essential question remains regarding the selection of patients and timing for surveillance.

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MINIREVIEWS

Colorectal cancer surveillance in inflammatory bowel disease: A critical analysis

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Abstract

Colonoscopic surveillance is advocated in patients with inflammatory bowel disease (IBD) for detection of dysplasia. There are many issues regarding surveillance in IBD: the risk of colorectal cancer seems to be decreasing in the majority of recently published studies, necessitating revisions of surveillance strategy; surveillance guidelines are not based on concrete evidence; commencement and frequency of surveillance, cost-effectiveness and adherence to surveillance have been issues that are only partly answered. The traditional technique of random biopsy is neither evidence-based nor easy to practice. Therefore, highlighting abnormal areas with newer technology and biopsy from these areas are the way forward. Of the newer technology, digital mucosal enhancement, such as high-definition white light endoscopy and chromoendoscopy (with magnification) have been incorporated in guidelines. Dyeless chromoendoscopy (narrow band imaging) has not yet shown potential, whereas some forms of digital chromoendoscopy (i-Scan more than Fujinon intelligent color enhancement) have shown promise for colonoscopic surveillance in IBD. Other techniques such as autofluorescence imaging, endomicroscopy and endocytoscopy need further evidence. Surveillance with genetic markers (tissue, serum or stool) is at an early stage. This article discusses changing epidemiology of colorectal cancer development in IBD and critically evaluates issues regarding colonoscopic surveillance in IBD.

Key words: Advanced imaging; Chromoendoscopy; Colorectal cancer; Colorectal cancer surveillance; Inflammatory bowel disease

Core tip: There is an increase in the risk of colorectal cancer in patients suffering from inflammatory bowel disease. Recent studies have suggested that this risk may be decreasing. In view of the risk, colonoscopic surveillance is recommended in order to detect cancer early. Instead of using previous methods of colonoscopy and random biopsy, newer technology such as chromoendoscopy and biopsy from abnormal mucosa is preferable.

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CHANGING EPIDEMIOLOGY OF COLORECTAL CANCER IN INFLAMMATORY BOWEL DISEASE

The risk of colorectal cancer (CRC) in patients with inflammatory bowel disease (IBD) was recognized as far back as 1925 for ulcerative colitis (UC) and 1948 for

Crohn's disease (CD)[1,2]. In the second half of the last century, attempts were made to quantify the actual risk of CRC in this population. Earlier studies, mainly in UC patients, tended to overestimate the risk, with cumulative cancer rates reportedly ranging from 16% to 43%[3-7]. A widely cited meta-analysis of 116 studies with age stratified data by Eaden *et al*[8] in 2001 estimated CRC risk as 2% at 10 years, 8% at 20 years and 18% at 30 years. In 2006, two landmark studies suggested a decreasing trend of CRC in IBD. Jess *et al*[9] reported a population-based estimate of CRC in IBD from Olmsted County, Minnesota, US. They reported that the risk of CRC was not increased in UC as compared to the general population [standardized incidence rate (SIR) 1.1; 95%CI: 0.4-2.4], but the risk of CRC was increased in CD (SIR 1.9; 95%CI: 0.7-4.1); the cumulative cancer risk was 2% at 20 years. The other study by Rutter *et al*[10] from St. Marks Hospital, United Kingdom, reported a CRC risk of 2.5% at 20 years, 7.6% at 30 years and 10.8% at 40 years, which was less than that reported by Eaden *et al*[8]. The lower risk of CRC was confined to a location proximal to the splenic flexure, but not at other locations. There were two subsequent meta-analyses. The study by Jess *et al*[11] in 2012 shortlisted eight population-based studies from 1958 to 2004 and reported a risk of 1.6% in patients with UC over 14 years of follow-up; UC increased the risk of CRC 2.4-fold (pooled SIR 2.4, range: 1.05-3.1; 95%CI: 2.1-2.7). The meta-analysis by Lutgens *et al*[12] also shortlisted eight studies from 1988 to 2009 and reported that the risk of CRC was increased in IBD, but was not as high as reported in earlier studies; the pooled SIR was 1.7 (CI: 1.2-2.2). Two recent studies came to different conclusions. In a population-based study from Denmark, Jess *et al*[13] suggested that the risk of colon cancer in UC is not as high as previously reported and in fact may not differ from the general population. To the contrary, Herrinton *et al*[14] showed that the risk of CRC in UC is 60% higher than in age- and gender-matched cohorts of people without IBD from California, and the risk remained the same throughout the study period of 14.5 years. Studies from Asia on CRC in UC are few, and report that the likelihood ranges from 0.87% to 1.8% in general, and can be as high as 13.5% in patients with extensive colitis[15-21].

The risk of CRC in CD was initially underestimated because of failure to evaluate cases of colitis as a separate risk group and to account for the effect of early colectomy. It is now established that patients with colonic or ileocolonic CD have an increased risk of CRC compared to the general population. A meta-analysis of 12 population- and hospital-based studies published in 2006 confirmed an overall relative risk (RR) of 2.5 (95%CI: 1.3-4.7) and an RR of 4.5 in those with colonic CD (95%CI: 1.3-14.7)[13]. The risk for those with ileal disease only was the same as the general population. Regardless of disease distribution, the cumulative risk of CRC was 2.9% after 10 years, 5.6% after 20 years, and 8.3% after 30 years of disease.

Thus, the risk of CRC is increased in IBD, though there is variation due to various factors such as referral center bias, population- or hospital-based data, and small numbers of patients. Prevalence rates of CRC in UC vary from 0.7% to 3.3%[9,22-28] and the cumulative risk is 1%, 2% and 5% for 10, 20, and > 20 years of disease duration, respectively, and a pooled SIR of 1.7 in all patients with IBD in population-based studies[13]. Table 1 summarizes the risk of CRC in IBD in various population groups. The surveillance strategy needs to take into account this decreasing risk of CRC in IBD.

GUIDELINES FOR SURVEILLANCE OF CRC IN IBD

Guidelines by various societies suggest that surveillance for CRC should begin after 8-10 years of disease duration. The guidelines include those from the American Gastroenterological Association (AGA; 2004 and 2010), Association of Coloproctology for Great Britain and Ireland (2004 and 2010), British Society of Gastroenterology (BSG; 2002 and 2010), National Institute for Health and Clinical Excellence (2011), European Crohn's and Colitis Organization (2013), and Australian (2011) and Austrian societies[29-34]. Table 2 summarizes the guidelines with changes over time. The salient features of the guidelines include that surveillance is advised 8-10 years after the onset of symptoms, irrespective of the extent (surveillance is not advised in patients with proctitis and proctosigmoiditis). The frequency of surveillance varies amongst the guidelines: AGA guidelines initially suggest surveillances every 1-2 years, and if two examinations are negative, then every 1-3 years up to the end of the second decade, after which the surveillance is again every 1-2 years. In the BSG guidelines, the frequency of surveillance depends upon the risk. Lower risk requires surveillance every 5 years, which includes extensive colitis with no endoscopic or histologic inflammation, left-sided colitis or crohn' s colitis (involving < 50% colon). Surveillance every three years is recommended for intermediate risk, which includes extensive colitis with mild active endoscopic, histologic inflammation, post inflammatory polyps, or family history of CRC in first-degree relatives over 50 years of age. Yearly surveillance is needed for those with higher risk, including extensive colitis with moderate or severe endoscopic or histologic inflammation, stricture or dysplasia in the past five years where patients have declined surgery, primary sclerosing cholangitis, or family history of CRC in a first-degree relative less than 50 years of age (surveillance yearly). The method of surveillance also varies, from random biopsy every 10 cm, which is still advocated, though the preferred method is to use chromoendoscopy and magnification and take biopsies from the abnormal areas.

Comparison of American and British guidelines

Mooiweer *et al*[35] from the Netherlands compared the American and British guidelines in a retrospective study of 1018 patients. They concluded that BSG surveillance intervals offer the advantage of a lower colonoscopic

Table 1 Risk of colorectal cancer in inflammatory bowel disease

Ref.	Type of study	Risk in UC	Risk in CD	Odds ratio (95%CI)	Comments
Eaden *et al*[8] 2001	Meta-analysis 116 studies; 41 mentioned duration of UC	3.7%		NA	2% at 10 yr, 8% at 20 yr, 18% at 30 yr
Jess *et al*[9] 2006	Population-based	6/378 (1.6%)	6/314 (1.9%)	SIR UC: 1.1 (0.4-2.4) CD: 1.9 (0.7-4.1)	Cumulative cancer risk 2% at 20 yr
Rutter *et al*[10] 2006	Hospital-based retrospective	3/600 (0.5%)	NA	NA	2.5% at 20 yr, 7.6% at 30 yr, 10.8% at 40 yr
Jess *et al*[11] 2012	Meta-analysis of 8 population-based (1958-2004)	1.6% (14 yr follow-up)	NA	Pooled SIR: 2.4 (2.1-2.7)	Risk of in patients with UC over
Lutgens *et al*[12] 2013	Meta-analysis (1988-2009)			IBD pooled SIR Population based: 1.7 (1.2-2.2) Referral based: 5.3 (2.8-7.8)	
Jess *et al*[13] 2012	Population-based			RR for CRC- UC 1979-1988: 1.34 (1.13-1.58) 1989-1998: 1.09 (0.9-1.33) 1999-2008: 0.57 (0.41-0.80) RR for CRC in CD: 0.85 (0.67-1.07), which did not change over time	CRC risk in UC reduced over three decades and comparable to general population; CD no change
Herrinton *et al*[14] 2012	Hospital-based	UC 53 /10895 CD 29/5603		UC: 1.6 (1.3-2.0) CD: 1.6 (1.2-2.0)	CRC risk in UC and CD 60% higher than population
Asian studies					
Gilat *et al*[15] 1988	Population-based (central Israel)		NA		CRC risk in UC: 0.2% at 10 yr, 5.5% at 20 yr, 13.5% at 30 yr
Kochhar *et al*[16] 1992	Hospital-based (India)	UC 1.8%	NA		
Venkataraman *et al*[17] 2005	Hospital-based (India)	UC 0.94%			
Kim *et al*[19] 2009	Population-based (South Korea)	UC 0.50%			
Kekilli *et al*[20] 2010	Hospital-based (Turkey)	UC 1.10%			
Gong *et al*[21] 2012	Hospital-based (China)	UC 0.87%			

CD: Crohn's disease; FH: Family history; IBD: Inflammatory bowel disease; NA: Not applicable; PSC: Primary sclerosing cholangitis; RR: Relative risk; SIR: Standardized incidence rate; UC: Ulcerative colitis.

workload (421 colonoscopies as per BSG guidelines and 541 colonoscopies as per AGA guidelines). However, the risk stratification of the AGA appears superior in distinguishing patients at higher risk of colitis-associated neoplasia (AGA: 5.3 and 20.3% in low and high risk groups, respectively; BSG: 3.6, 6.9 and 10.8% in low, intermediate and high-risk groups, respectively).

ISSUES WITH SURVEILLANCE

Is surveillance really necessary?

Most of the above guidelines suggest that surveillance is recommended based on the high risk of CRC in IBD[8]. However, a recent study by Jess *et al*[13] suggested that the incidence of CRC in UC in a Dannish population decreased over 30 years (1979-2008), and the risk was not different from the general population during the period of 1999-2008 (RR 0.8). There is no systematic surveillance in Denmark. In their population-based study from patients in the US, Jess *et al*[9] reported no overall increase in CRC in all UC patients but only in patients with extensive colitis. A Dannish article commented that, based on Dannish epidemiologic data, the American and British recommendations were dubious and surveillance may be recommended in patients with extensive, uncontrolled inflammation and patients with primary sclerosing cholangitis, and not on the disease duration[36]. Thus, although surveillance is recommended by all societies, routine surveillance may not be beneficial and surveillance strategies should be reviewed due to the reduction in risk of CRC in UC.

When should surveillance begin?

The guidelines suggest that surveillance for CRC should begin after 8-10 years of disease duration. However, if these recommendations are followed, CRC is likely to be missed. In the study by Gilat *et al*[15], 2/26 patients who developed CRC in UC had a disease duration less than ten years (six and nine years)[16]. The cumulative risk of CRC in the first decade was 1.15% in the study by Gong *et al*[21], and 1.6% in the meta-analysis by Eaden *et al*[8]. Lutgens *et al*[37] reported that 15% of their patients with UC developed CRC before the recommended surveillance period. Kocher *et al*[16] reported that 2/8 patients developed CRC at seven and eight years of disease duration. Thus, we are faced with a dilemma: on one hand, the incidence seems to be decreasing, whereas on the other hand, we are likely to miss about 15%-20% of patients who develop CRC before the recommended commencement of surveillance.

Table 2 Guidelines of various societies on surveillance for colorectal cancer in ulcerative colitis

Society	Year	Beginning of surveillance	Frequency	Technique	Biopsy protocol	Risk	Change
BSG	2002	All patients have colonoscopy screening at 8-10 yr; surveillance begins 8-10 yr after onset for pancolitis, 15-20 yr for left-sided colitis	Decrease in surveillance interval with increase in disease duration for pancolitis: Every 3 yr: 2nd decade Every 2 yr: 3rd decade Every 1 yr: 4th decade	Nil	2-4 random biopsies every 10 cm from the entire colon	Patients with PSC, including those with OLT, should have annual screening	
AGA	2004	8-10 yr	Every 1-2 yr	Nil			
ACG	2004	8-10 yr	Every 1-2 yr	Nil			
ECCO	2008	8 yr for pancolitis, 15 yr for left-sided colitis	Every 2 yr: 1st two decades Every 1 yr: 3rd decade	CE			
BSG	2010	10 yr	Based on extent of disease, endoscopic and histologic activity, FH of CRC, presence of PSC, pseudopolyps, stricture, dysplasia on biopsy: Every 3 yr: low risk Every 2 yr: intermediate risk Every 1 yr: high risk	CE	Random biopsies every 10 cm and biopsies from raised/ suspicious areas on CE	Patients with PSC, including those with OLT, should have annual screening	If dysplastic polyp within area of inflammation can be removed entirely, colectomy is not necessary
AGA	2010	8-10 yr	Every 1-2 yr If two examinations are negative, then every 1-3 yr up to 20 yr, then every 1-2/yr	CE		Patients with PSC, including those with OLT, should have annual screening	
NICE	2011	10 yr	As per BSG 2010 guidelines	CE			
Australian	2011	8-10 yr	As per BSG 2010 guidelines	CE			
ECCO	2013	6-8 yr, 8-10 yr	Same as BSG	CE			

ACG: Association of Coloproctology for Great Britain and Ireland; AGA: American Gastroenterological Association; BSG: British Society of Gastroenterology; CE: Chromoendoscopy; CRC: Colorectal cancer; ECCO: European Crohn's and Colitis Organization; FH: Family history; NICE: National Institute for Health and Clinical Excellence; OLT: Orthotopic liver transplantation; PSC: Primary sclerosing cholangitis.

ROLE OF NEWER MODALITIES FOR SURVEILLANCE IN IBD

There are clear lapses in the present form of colonoscopic surveillance. The random biopsy technique is not very useful for detecting dysplasia. In a retrospective analysis of 11772 biopsies in 466 colonoscopies in 167 patients over ten years, this technique had a much lower yield of dysplasia as compared to targeted biopsies and did not significantly change the management[38,39]. Two retrospective studies have shown that dysplasia in IBD is macroscopically visible in 72%-77% of patients[40,41]. Based on a single retrospective study, high-definition endoscopy is three times more likely to detect dysplastic lesions as compared to standard-definition endoscopy[42].

Chromoendoscopy and magnification chromoendoscopy have been used for the detection of dysplastic lesions that are likely to be missed by white light endoscopy. A meta-analysis of six studies showed that the yield with chromoendoscopy was 7% greater than that of white light endoscopy, and the pooled increase in targeted dysplasia detection of chromoendoscopy over white light endoscopy was 44% (95%CI: 28.6-59.1)[43]. The difference in detection of flat dysplastic lesions was 27% (95%CI: 11.2-41.9). Chromoendoscopy has been incorporated in the recent guidelines.

Dyeless chromoendoscopy includes compound-band imaging and narrow-band imaging, which fails to detect dysplasia in patients with IBD and has not been recommended for surveillance in its present form[39]. Digital chormoendoscopy includes i-Scan and Fuji intelligent chromoendoscopy, which have not been studied in clinical trials in IBD patients to detect dysplasias. They have been used to detect adenomas in surveillance programs in CRC in a non-IBD population, where only i-Scan demonstrated some positive results[39]. Studies using autofluorescence imaging have shown that it is a sensitive modality to detect dysplastic lesions in IBD[44]. Confocal laser endomicroscopy and endocytoscopy allow for magnification of up to 1390-fold. Confocal laser endomicroscopy detects more dysplasia than white light and chromoendoscopy, but requires special training and takes twice as much time[45,46]. Table 3 summarizes the important features of these modalities.

Although the pathogenesis of CRC in IBD differs from sporadic CRC, polyposis syndromes and hereditary non-polyposis colon cancers, the pathways include chromosomal instability, microsatellite instability and CpG island methylation pathways. Tissue-based markers, such as aneuploidy, p53, and microsatellite instability, are associated with the development of dysplasia or CRC[30]. They cannnot be included in the guidelines for surveillance for CRC in IBD at present.

NON-COLONOSCOPIC APPROACHES FOR CANCER SURVEILLANCE IN IBD

Non-colonoscopic techniques that are noninvasive are

Table 3 Endoscopic dysplasia-detection modalities in patients with inflammatory bowel disease and recommendations for use[39]

	Demonstrated accuracy in IBD	Supporting evidence in IBD	Incorporated into guidelines	Practicality of use in practice	Should be used in 2013?
Random biopsy	-	-	+	±	±
HD WLE	+	±	+	+	+
Chromoendoscopy	+	+	+	+	+
NBI	-	-	-	±	-
FICE	NA	NA	-	±	-
i-Scan	NA	NA	-	±	-
AFI	+	+	-	-	-

AFI: Auto-fluorescence imaging; HD WLE: High-definition white light endoscopy; FICE: Fuji intelligent chromoendoscopy; IBD: Inflammatory bowel disease; NA: Not available; NBI: Narrow-band imaging. Reproduced with permission[39].

more appealing to patients than the repeated invasive colonoscopic approach, with the potential to reduce the high cost associated with surveillance. Stool examination has been used for surveillance for sporadic CRC and stool DNA testing has recently been incorporated[47]. Studies by Kisiel and others suggest that stool DNA testing is feasible to detect CRC in patients with IBD[48,49]. Although this approach is not recommended for surveillance at present, it has the potential to radically change the approach to surveillance.

IS SURVEILLANC EFFECTIVE? DOES SURVEILLANCE SAVE LIVES? IS IT COST-EFFECTIVE?

Multiple case series and case control studies have suggested that surveillance leads to improvement in survival in UC, which was not supported by a Cochrane systematic review[50-58]. The data from the Cochrane analysis suggests that there is no clear evidence that surveillance colonoscopy prolongs survival in patients with extensive colitis. In patients undergoing surveillance, CRC is detected at an earlier stage, which may lead to a better prognosis (which may actually be due to lead-time bias). Surveillance may be effective in reducing the risk of death and it may be cost-effective. These findings have to be taken with the facts that these pivotal studies were in the 1990s, and the Cochrane analysis was in 2004. Studies showing a reduction in CRC have been published after these studies and this analysis may not hold true in the situation with reduced risk of CRC in UC. Surveillance is advocated in CD but there is no data to support it[30].

ADHERENCE OF PHYSICIANS AND PATIENTS TO SURVEILLANCE COLONOSCOPY

There is a wide variation in conducting colonoscopic surveillance by gastroenterologists. Eaden *et al*[59] reported that all British gastroenterologists perform colonoscopic surveillance in pancolitis, but only 24% practiced surveillance in left-sided colitis, and only 2% took more than 20 biopsies. In a survey from the Netherlands, 95% of gastroenterologists performed colonoscopic surveillance in UC and 65% in CD; a majority (73%) of gastroenterologists took fewer than 30 biopsies, and only 27% followed AGA guidelines[60]. From this and similar data, it is clear that the concept of colonoscopic surveillance is accepted by gastroenterologists in general, but there are lapses in the frequency of surveillance and in taking the requisite number of biopsies. Targeted biopsies may reduce this problem. Friedman *et al*[61] studied patient-related factors in colonoscopic surveillance and reported that only one-fourth of their patients underwent surveillance colonoscopy at an interval of less than three years; the factors related to non-adherence were logistics, health perceptions, stress regarding procedure, job or personal life, and procedural problems. The most frequent patient-related reason was difficulty with bowel preparation.

CONCLUSION

Should surveillance be continued in same way today or should we change it? It is clear that colonoscopic surveillance in the present form is neither an ideal nor practical approach. We feel that in the light of new data, the guidelines need to be re-examined. The surveillance should likely begin at six years after the onset of symptoms. It should consist of high-definition white light endoscopy with magnification chromendoscopy and with targeted, rather than random, biopsies. The frequency of surveillance is not clear. In view of the recent comparison of American and British guidelines, further studies are necessary to decide frequency of surveillance. At present, British guidelines are useful, considering the fact that the risk of CRC is decreasing in UC. But there are ambuguities in both guidelines. As the techology evolves, it should be incorporated in surveillance (after considering cost-effectiveness): digital chromoendoscopy seems to come close to this. Other new technologies seem many years away.

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META-ANALYSIS

Hyoscine for polyp detection during colonoscopy: A meta-analysis and systematic review

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Abstract

AIM: To assess the role of hyoscine for polyp detection during colonoscopy.

METHODS: Studies (randomized controlled trials or RCTs) that compared the use of hyoscine *vs* no hyoscine or placebo for polyp detection during colonoscopy were included in our analysis. A search on multiple databases was performed in September 2013 with search terms being "hyoscine and colonoscopy", "hyoscine and polyp", "hyoscine and adenoma", "antispasmotic and colonoscopy", "antispasmotic and adenoma", and "antispasmotic and polyp". Jadad scoring was used to assess the quality of studies. The efficacy of hyoscine was analyzed using Mantel-Haenszel model for polyp and adenoma detection with odds ratio (OR). The I^2 measure of inconsistency was used to assess heterogeneity ($P < 0.05$ or $I^2 > 50\%$). Statistical analysis was performed by RevMan 5.1. Funnel plots was used to assess publication bias.

RESULTS: The search of the electronic databases identified 283 articles. Of these articles, eight published RCTs performed at various locations in Europe, Asia, and Australia were included in our meta-analysis, seven published as manuscripts and one published as an abstract ($n = 2307$). All the studies included patients with a hyoscine and a no hyoscine/placebo group and were of adequate quality (Jadad score ≥ 2). Eight RCTs assessed the polyp detection rate (PDR) ($n = 2307$). The use of hyoscine demonstrated no statistically significant difference as compared to no hyoscine or placebo for PDR (OR = 1.06; 95%CI: 0.89-1.25; $P = 0.51$). Five RCTs assessed the adenoma detection rate (ADR) ($n = 2015$). The use of hyoscine demonstrated no statistically significant difference as compared to no hyoscine or placebo for ADR (OR = 1.12; 95%CI: 0.92-1.37; $P = 0.25$). Furthermore, the timing of hyoscine administration (given at cecal intubation or pre-procedure) demonstrated no differences in PDR compared to no hyoscine or placebo. Publication bias or heterogeneity was not observed for any of the outcomes.

CONCLUSION: Hyoscine use in patients undergoing colonoscopy does not appear to significantly increase the detection of polyps or adenomas.

Key words: Hyoscine; Antispasmodic; Polyp detection; Colonoscopy

Core tip: Hyoscine is used in clinical practice to decrease spasms in the colon during colonoscopy in an effort to improve polyp or adenoma detection. However, this study shows that hyoscine given before the procedure or at time of cecal intubation does not improve polyp or adenoma detection.

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INTRODUCTION

Colorectal cancer (CRC) is a common and devastating condition with higher incidence in developed countries/western world[1-4]. Screening programs have reduced the mortality related to CRC[5-7]. Most of these cancers arise from adenomatous polyps which can later progress into dysplasia and cancer; referred to as the adenoma-carcinoma sequence[8]. Colonoscopy is an important screening tool and has a large part in the reduction of CRC occurrence by removing these adenomatous polyps[9].

Adenoma detection rate (ADR) and polyp detection rate (PDR) are pivotal indicators for a quality colonoscopy and inversely related to the development of interval carcinoma[10,11]. Many polyps are missed with colonoscopy because of various factors, such as bowel preparation quality[12,13], polyp position[14,15], and colonic spasm[16,17]. Different antispasmodic agents including glucagon[18], dicyclomine[19], and atropine[20] have shown no significant benefit to facilitate colonoscopy.

Hyoscine butylbromide is a relatively safe antispasmodic anticholinergic agent which is commercially available in many forms (sublingual, injectable, and pills) and is frequently used to treat patients with functional bowel pain[21]. It blunts the response of colonic neurons to muscarinic and nicotinic stimulation which leads to inhibition of smooth muscle contraction in the colon[22]. It is associated with significantly less anticholinergic side effects due to not crossing the blood-brain barrier, making it a useful antispasmodic agent[23].

The use of hyoscine as premedication or at the time of cecal intubation during colonoscopy has shown conflicting results for detection of polyps[17,24-30]. Therefore, through study of randomized controlled trials (RCTs), hyoscine was compared to no hyoscine or placebo for polyp or adenoma detection during colonoscopy.

MATERIALS AND METHODS

Study selection

RCTs comparing hyoscine to no hyoscine or placebo on adults for polyp detection during colonoscopy were included. Criteria for exclusion was pediatric patients, non-randomized controlled trials, and abstract publications from other than the American College of Gastroenterology (ACG) and Digestive Disease Week (DDW) meetings or prior to 2003.

Data collection and extraction

Data was collected in multiple stages. First, a comprehensive search of PubMed/Medline, Embase, Cochrane databases, and CINAHL in September 2013 was conducted. Second, each selected article's references were searched. Lastly, abstracts of DDW and ACG national meetings were searched from 2003-2013. The keywords used for the search included "hyoscine and colonoscopy", "hyoscine and polyp", "hyoscine and adenoma", "antispasmotic and colonoscopy", "antispasmotic and adenoma", and "antispasmotic and polyp". Standard forms were utilized for data extraction by three authors (IA, SA, and MLB) independently with any disagreements ruled on by a fourth author (AC) or mutual agreement. If data was incomplete or unclear, authors were contacted. Study quality was assessed by a Jadad score[31,32]. Jadad score ranges from 0 (poor quality) to 5 (excellent quality)[31]. It evaluates multiple study parameters related to randomization, blinding, and withdrawals. One point is deducted for each inappropriate criterion[31].

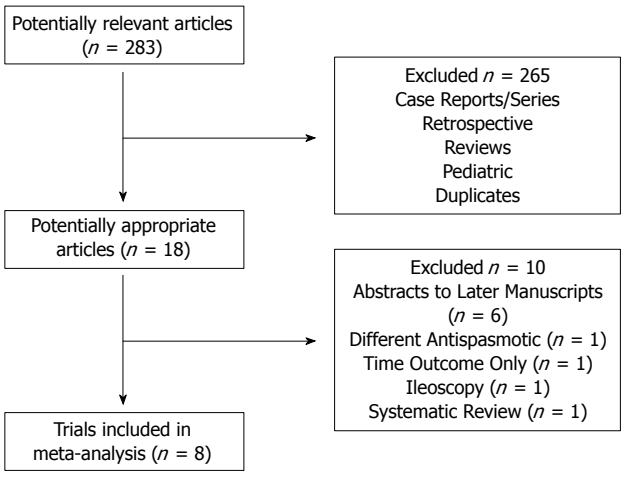

Figure 1 Selection of studies for inclusion in the meta-analysis.

Statistical analysis

Pooled estimates of PDR and ADR were calculated for the effect of hyoscine or no hyoscine or placebo by odds ratio (OR) with Mantel-Haenszel (fixed effect) model given no heterogeneity identified.

Furthermore, a subgroup analysis was performed in similar fashion for the timing of the hyoscine administration, pre-procedure or during colonoscopy upon cecal intubation. I^2 measure of inconsistency was used to assess heterogeneity (significant if $P < 0.05$ or $I^2 > 50\%$). Statistics performed by RevMan 5.1 (Review Manager Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Funnel plots, Egger's regression intercept and Begg-Mazumdar rank correlation methods assessed publication bias.

RESULTS

Search of the electronic databases identified 283 articles (Figure 1). Of these articles, 8 published randomized controlled trials (RCTs) performed at various locations in Europe, Asia, and Australia were included in our meta-

Table 1 Characteristics of studies included in meta-analysis

Ref.	Study type	Blinding	Location	No. of patients	Hyoscine dose	Hyoscine route	Timing of administration
de Brouwer *et al*[26] 2012	RCT	Double	Netherlands	674	20 mg	IV	Cecal intubation
Byun *et al*[24] 2009	RCT	Double	NR	205	20 mg	IV	Cecal intubation
Lee *et al*[17] 2010	RCT	Double	NR	116	20 mg	IV	Cecal intubation
Kim *et al*[27] 2010	RCT	Double	South Korea	133	20 mg	IM	Premedication
Rondonotti *et al*[29] 2013	RCT	Double	Italy	402	20 mg	IV	Cecal intubation
Mui *et al*[28] 2004	RCT	Yes	China	120	40 mg	IV	Premedication
Saunders *et al*[30] 1996	RCT	Yes	England	56	20 mg	IV	Premedication
Corte *et al*[25] 2012	RCT	Yes	Australia	601	20 mg	IV	Cecal intubation

RCT: Randomized controlled trial; NR: Not reported.

Table 2 Quality assessment of the studies included in this meta-analysis using Jadad scale

Ref.	Study design	Method of randomization	Double-blind	Method of double-blinding	Description of withdrawals	Total score[2]
de Brouwer *et al*[26] 2012	1	1	1	0	1	4
Byun *et al*[24] 2009[1]	1	0	1	0	1	3
Lee *et al*[17] 2010	1	1	1	0	1	4
Kim *et al*[27] 2010	1	0	1	0	1	3
Rondonotti *et al*[29] 2013	1	1	1	1	1	5
Mui *et al*[28] 2004	1	1	1	1	1	5
Saunders *et al*[30] 1996	1	1	1	1	1	5
Corte *et al*[25] 2012	1	1	1	1	1	5

[1]Abstract; [2]Jadad Score: 1-5, 5 is excellent and 1 is poor.

analysis, seven published as manuscripts[17,25-30] and one published as an abstract[24] (Table 1). All included patients with a hyoscine and a no hyoscine/placebo group and were of acceptable quality (≥ 2 on the Jadad scale) (Table 2).

Polyp detection rate

Eight RCTs assessed the polyp detection rate (PDR) (n = 2307). The use of hyoscine demonstrated no statistically significant difference as compared to no hyoscine or placebo for PDR (502/1165, 43.1% *vs* 478/1142, 41.9%; OR = 1.06; 95%CI: 0.89-1.25; P = 0.51) (Figure 2). Statistically significant heterogeneity was not observed (I^2 = 45%, P = 0.51).

Adenoma detection rate

Five RCTs assessed the adenoma detection rate (ADR) (n = 2015). The use of hyoscine demonstrated no statistically significant difference as compared to no hyoscine or placebo for ADR (294/1018, 28.9% *vs* 266/997, 26.7%; OR = 1.12; 95%CI: 0.92-1.37; P = 0.25) (Figure 3). No heterogeneity was observed (I^2 = 17%, P = 0.25).

Timing of hyoscine administration

On subgroup analysis, hyoscine administration given at cecal intubation showed no statistically significant difference in polyp (467/1006, 46.4% *vs* 435/996, 43.7%; OR = 1.12; 95%CI: 0.94-1.34; P = 0.22) or adenoma detection rate (287/948, 30.3% *vs* 256/934, 27.4%; OR = 1.15; 95%CI: 0.94-1.41; P = 0.17) as compared to no hyoscine or placebo. Furthermore, hyoscine administration pre-procedure showed no difference in PDR (35/159, 22% *vs* 43/150, 28.7%; OR = 0.71; 95%CI: 0.42-1.19; P = 0.19).

Publication bias

Publication bias was not observed as measured with funnel plot, Egger's regression intercept method, or Begg-Mazumdar rank correlation method (Figure 4).

DISCUSSION

CRC is a preventable and curative condition if diagnosed early in the premalignant polyp stage. The quality of colonoscopy is very important as many polyps may be missed during screening colonoscopies which can lead to the development of interval carcinoma at a later stage[33]. Currently, ADR is considered one of the core parameters of a quality screening colonoscopy and better ADR can lead to decreased incidence of interval carcinoma[34].

Different medications including glucagon[18], dicyclomine[19], and atropine[20] have been tried to facilitate the colonoscopic exam with no significant improvement in results. Of all these agents, hyoscine has been evaluated extensively in RCTs with conflicting outcomes. Lee *et al*[17] found better PDR with the use of hyoscine with significant decrease in the colonic spasm. They did not notice any difference between the sites of polyps and suggested that hyoscine might be an option in patients with significant spasm[17]. Similarly, Corte *et al*[25] favored the use of hyoscine for screening and surveillance colonoscopy to aid in polyp detection. They did notice a difference in the withdrawal time and attributed that likely to the time spent on waiting for the spasm to resolve[25]. However, this was not designed primarily for ADR and considered

Study or subgroup	Favors hyoscine Events	Total	Favors placebo Events	Total	Weight	Odds ratio M-H, fixed, 95%CI
Byun *et al*-2009	47	103	36	102	7.5%	1.54 (0.88, 2.70)
Corte *et al*-2012	132	303	109	298	23.8%	1.34 (0.96, 1.86)
de brouwer *et al*-2012	190	340	201	334	34.3%	0.84 (0.62, 1.14)
Kim *et al*-2010	11	70	18	63	6.1%	0.47 (0.20, 1.08)
Lee *et al*-2010	20	58	15	58	3.8%	1.51 (0.68, 3.35)
Mui *et al*-2004	16	60	21	60	5.9%	0.68 (0.31, 1.47)
Rondonotti *et al*-2013	78	202	74	200	17.5%	1.07 (0.72, 1.60)
Saunders *et al*-1996	8	29	4	27	1.1%	2.19 (0.57, 8.35)
Total (95%CI)		1165		1142	100.0%	1.06 (0.89, 1.25)
Total events	502		478			

Heterogeneity: χ^2 = 12.70, df = 7 (P = 0.08); I^2 = 45%

Test for overall effect: Z = 0.66 (P = 0.51)

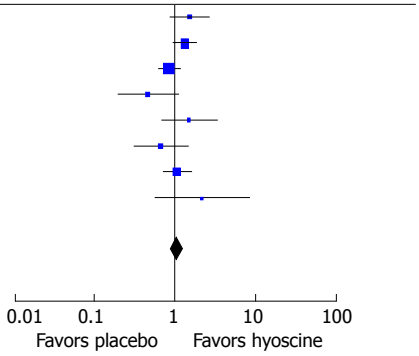

Figure 2 Forest plot showing no statistically significant difference in polyp detection rate between hyoscine and placebo group.

Study or subgroup	Favors hyoscine Events	Total	Favors placebo Events	Total	Weight	Odds ratio M-H, fixed, 95%CI
Byun *et al*-2009	40	103	30	102	9.8%	1.52 (0.85, 2.73)
Corte *et al*-2012	82	303	65	298	25.3%	1.33 (0.92, 1.93)
de brouwer *et al*-2012	101	340	105	334	39.5%	0.92 (0.66, 1.28)
Kim *et al*-2010	7	70	10	63	5.0%	0.59 (0.21, 1.65)
Rondonotti *et al*-2013	64	202	56	200	20.4%	1.19 (0.78, 1.83)
Total (95%CI)		1018		997	100.0%	1.12 (0.92, 1.37)
Total events	294		266			

Heterogeneity: χ^2 = 4.82, df = 4 (P = 0.31); I^2 = 17%

Test for overall effect: Z = 1.15 (P = 0.25)

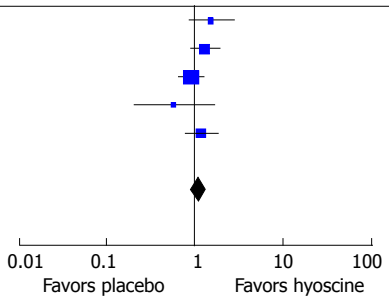

Figure 3 Forest plot showing no statistically significant difference in adenoma detection rate between hyoscine and placebo group.

PDR to be a surrogate marker for adenoma detection[25]. Despite these studies favoring the use of hyoscine to facilitate colonoscopy and polyp detection, other studies have showed contradictory results.

Byun *et al*[24] discovered no difference in polyp or ADR with more side effects with hyoscine use. Furthermore, procedure time and spasm score were not affected[24]. Similarly, de Brouwer *et al*[26] found no difference in PDR, ADR, or advanced lesions (> 1 cm) between the two groups. They did not appreciate any difference in withdrawal time between the two groups either but their study included gastroenterologists with more than 10-years' experience[26]. More recently, Rondonotti *et al*[29] found similar results in a well-designed randomized controlled trial with no differences in ADR or advanced adenomas. Their findings rather opposed the use of hyoscine because of the lower detection of flat lesions with no difference in the procedure tolerance between the two groups[29]. Given that the results are conflicting and the high impact on performing a better colonoscopic exam, this meta-analysis was conducted.

An ideal antispasmodic agent should be able to decrease the total procedure time with better procedure tolerability, acceptable side effect profile, and should increase the polyp and adenoma detection rate. Although hyoscine is considered a relatively safe medication[35,36], Marshall *et al*[21] reported patients who developed sinus tachycardia with hyoscine. Similarly, Rondonotti *et al*[29] also reported an increased incidence of tachycardia in the hyoscine group. The finding of tachycardia in these studies lead to unblinding. Byun *et al*[24] also reported significant incidence of dry mouth with the use of hyoscine.

In this meta-analysis, hyoscine use did not show an increase in PDR or ADR during colonoscopy. No statistically significant differences between hyoscine *vs* no hyoscine or placebo in adenoma or polyp detection irrespective of timing of hyoscine administration (given at cecal intubation or pre-procedure). Recently, Cui *et al*[37] found similar results with a meta-analysis on this subject; however, it was limited to only five studies. Numerous strengths were apparent in this meta-analysis. First, a three-stage extensive article and abstract search was carried out. Second, various populations with a large number of patients were included. Third, the two main outcomes (adenoma and polyp detection) were evaluated in all included studies. Fourth, inclusion of high-quality positive and negative RCTs as evaluated by the Jadad score. Finally, publication bias was not observed. Despite the strengths, a few limitations are observed in our meta-analysis. First, timing of administration of hyoscine was different in these studies with some administering it as premedication while others gave it after cecal intubation (Table 1). Therefore, a subgroup analysis was performed to evaluate if timing made a difference and discovered

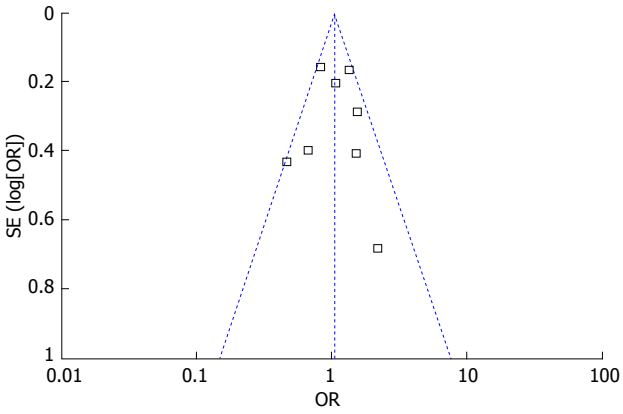

Figure 4 Funnel plot demonstrating no significant publication bias.

that timing did not impact the results. Second, Mui *et al*[28] used a slightly higher dose (40 mg) compared to other studies. However, it this study was removed, the results were unchanged. Third, Kim *et al*[27] administered hyoscine intramuscularly which may have a slightly different bioavailability compared to IV form. Again, when this study was removed, no changes were observed in the outcomes.

In conclusion, hyoscine use during colonoscopy does not increase the polyp or adenoma detection rate. Therefore, hyoscine should not be routinely used in an effort to increase polyp detection during colonoscopy.

COMMENTS

Background

The main purpose of colonoscopy is to identify adenomatous polyps and colorectal cancers. Given potential of colonic spasms during colonoscopy, many agents have been studied to decrease the spasms in an effort to improve the adenomatous detection rate (ADR). One such agent is hyoscine.

Research frontiers

Hyoscine has been studied by multiple randomized controlled trials as an adjunct medication before or during colonoscopy to enhance ADR.

Innovations and breakthroughs

The authors found that hyoscine administered before or during colonoscopy does not appear to improve polyp detection rate (PDR) or ADR.

Applications

This information may limit the use of hyoscine before or during colonoscopy.

Terminology

Odds ratio: Statistical term for the odds an event did or did not occur. Heterogeneity: Test for uniformity in composition of studies included. Publication bias: Phenomenon where positive studies are more published more than negative studies, leading to possible misrepresentation of data in meta-analysis. PDR: Having one or more polyps identified during a colonoscopy. ADR: Having one or more adenomatous polyps identified on colonoscopy.

Peer review

The manuscript focussed on hyoscine for polyp detection during colonoscopy. The manuscript is well written.

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META-ANALYSIS

Endoscopic submucosal dissection *vs* endoscopic mucosal resection for early gastric cancer: A meta-analysis

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Abstract

AIM: To compare endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) for early gastric cancer (EGC).

METHODS: Computerized bibliographic search was performed on PubMed/Medline, Embase, Google Scholar and Cochrane library databases. Quality of each included study was assessed according to current Cochrane guidelines. Primary endpoints were *en bloc* resection rate and histologically complete resection rate. Secondary endpoints were length of procedure, post-treatment bleeding, post-procedural perforation and recurrence rate. Comparisons between the two treatment groups across all the included studies were performed by using Mantel-Haenszel test for fixed-effects models (in case of low heterogeneity) or DerSimonian and Laird test for random-effects models (in case of high heterogeneity).

RESULTS: Ten retrospective studies (8 full text and 2 abstracts) were included in the meta-analysis. Overall data on 4328 lesions, 1916 in the ESD and 2412 in the EMR group were pooled and analyzed. The mean operation time was longer for ESD than for EMR (standardized mean difference 1.73, 95%CI: 0.52-2.95, P = 0.005) and the "*en bloc*" and histological complete resection rates were significantly higher in the ESD group [OR = 9.69 (95%CI: 7.74-12.13), $P < 0.001$ and OR = 5.66, (95%CI: 2.92-10.96), $P < 0.001$, respectively]. As a consequence of its greater radicality, ESD provided lower recurrence rate [OR = 0.09, (95%CI: 0.05-0.17), $P < 0.001$]. Among complications, perforation rate was significantly higher after ESD [OR = 4.67, (95%CI, 2.77-7.87), $P < 0.001$] whereas the bleeding incidences did not differ between the two techniques [OR = 1.49 (0.6-3.71), $P = 0.39$].

CONCLUSION: In the endoscopic therapy of EGC, ESD showed a superior efficacy but higher complication rate with respect to EMR.

Key words: Endoscopic submucosal dissection; Endoscopic mucosal resection; Early gastric cancer; Meta-analysis

Core tip: Endoscopic submucosal dissection (ESD) represents a promising approach to the therapy of Early Gastric Cancer. Preliminar studies showed better outcomes in terms of complete *en bloc* and histologic resection rate with respect to classical Endoscopic Mucosal Resection (EMR). Some concerns raise due to higher complication rate (particularly perforation) and longer operation times related to the complexity of the procedure. The current meta-analysis outline the superiority of ESD in obtaining higher radical resection rate and lower recurrence rates compared to EMR but confirms the aforementioned concerns on higher incidences of perforation and bleeding (in this case non significantly) after ESD.

Facciorusso A, Antonino M, Di Maso M, Muscatiello N. Endoscopic submucosal dissection *vs* endoscopic mucosal resection for early gastric cancer: A meta-analysis. *World J Gastrointest*

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INTRODUCTION

Early gastric cancer (EGC) is a malignant tumor confined to the mucosa or the submucosa regardless of lymph node metastases[1].

As the diagnostic rate of EGC increases, endoscopy has become the treatment of choice for the radical cure of EGC. Since the 1980s endoscopic mucosal resection (EMR) has been proposed as a replacement for invasive surgery because of favorable long-term outcomes and improved quality of life for patients[2,3]. EMR is routinely performed due to its safety profile, low cost, patient tolerance and rapid post-procedural recovery.

Endoscopic submucosal dissection (ESD) was developed in the late 1990s to enable the *en bloc* removal of lesions larger than 2 cm[4]. In fact, only a complete pathological specimen may allow clinicians to achieve a reliable diagnosis and hence to plan the correct therapeutic strategy.

ESD uses the technique of improved needle-knife under endoscopy to exfoliate the diseased submucosa with coagulation corrent.

Previous systematic reviews and meta-analyses have reported higher resection rates but also a relatively higher rate of complications such as bleeding and perforation after ESD because of its large wound incidence and difficulties[5,6]. Since these reviews date early 2010s, systematic analyses including pooled data of recent studies on this topic are lacking.

Aim of the current meta-analysis is to update the state of the art of endoscopic therapies of EGC in light of the last studies published in this field.

MATERIALS AND METHODS

Search strategy and selection criteria

Computerized bibliographic search was performed on PubMed/Medline, Embase, Google Scholar, Cochrane library databases using the following key words: "EMR", "ESD", "endoscopic mucosal resection", "endoscopic submucosal dissection" and "early gastric cancer". Complementary manual search was performed by checking the references of all the main review articles on this topic, in order to identify possible additional studies. Moreover, the abstracts of main oncological and endoscopic congresses were retrieved.

Eligible studies were randomized controlled trials, prospective or retrospective cohort and case-control studies and international congress abstracts comparing EMR and ESD for the treatment of EGC in human patients published until April 2014. The search was restricted to English-language articles. Studies were excluded if they had not compared data between the two treatments. Case reports or studies with insufficient data were also excluded. Included studies were selected independently by two investigators (AF and MA). Disagreements were solved by discussion and following a third opinion (MdM).

The quality of the included studies was assessed according to the guidelines of the Cochrane Reviewer's Handbook recommended by the Cochrane Collaboration[7].

Endpoints evaluated

Primary endpoints were: *en bloc* resection rate (*i.e.*, no piecemeal removal of the lesion)[8] and histologically complete resection rate (no neoplastic cells in lesion edges).

Secondary endpoints were: length of procedure (from marking to removal of the tumor); post-treatment bleeding; post-procedural perforation; and recurrence rate (diagnosed by histology within the treated area during follow-up).

Statistical analysis

Pooled data of continuous variables were expressed as standardized mean difference while data of categorical ones as odds ratio (OR) and 95%CI.

Comparisons between the two treatment groups across all the included studies were performed by using Mantel-Haenszel test for fixed-effects models[9] (in case of low heterogeneity) or DerSimonian and Laird test for random-effects models[10] (in case of high heterogeneity). The level of heterogeneity between the included studies was assessed following the guidelines of the Cochrane Collaboration[7]. Once heterogeneity was noted, between-study sources of heterogeneity were investigated using subgroup analyses by stratifying original estimates according to the study characteristics.

Since the use of scales for evaluating quality or risk of bias is explicitly discouraged in Cochrane reviews[7], in assessing study quality a domain-based evaluation was performed, in which critical assessments were made separately for different domains[7].

Publication biases were assessed using funnel plots visually and performing Begg and Mazumdar's test based on the rank correlation between the observed effect sizes and observed standard errors[11]. Whenever publication biases were found, "trim and fill" method was performed aiming at obviating to these biases.

Significance threshold was assessed at a P-value < 0.05.

All calculations were performed using Review Manager (version 5.0 for Windows; the Cochrane Collaboration, Oxford, United Kingdom) and R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Literature search

Figure 1 shows the flow chart of the search strategy conducted in this meta-analysis.

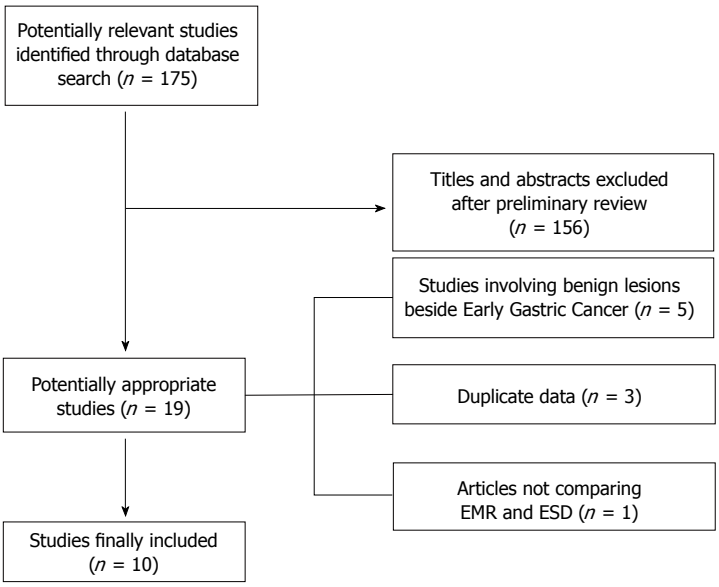

Figure 1 Flow chart of the search strategy. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

Initially, we identified 175 potentially relevant studies. After a preliminary review, 156 papers were excluded, because they were animal studies, case reports, comment letters or descriptive reviews.

Among 19 potentially appropriate articles, we excluded 5 studies[12-16] because did not examine EGC, 3 studies[17-19] because based on the same data and another one due to the lack of comparative results between the two treatments[20]. Finally, 10 studies[8,21-29] were included in the meta-analysis.

Characteristics of included studies

Main characteristics of included studies are shown in Table 1. The current meta-analysis analyzed reports of a total of 4328 lesions, 1916 in the ESD and 2412 in the EMR group. The included papers were all retrospective case-control studies, whereof 8 were full text articles[8,21-23,26-29] and 2 were abstracts[24,25].

In two studies data on the number of patients were not available[25,26], while in three articles[24-26] median follow-up times were not recorded. The studies in which demographic and tumoral baseline parameters were reported did not show significant differences between treatment groups thus obviating to selection biases that could have affect final outcomes. Quality assessment of each study can be seen in Figure 2.

Operation time

Mean length of the procedures was described in four studies[21,22,26,27]. As an high grade of heterogeneity was found ($P < 0.001$; $I^2 = 99\%$), a random effect model was applied. Mean operation time was significantly longer in the ESD group [overall standardized mean difference 1.73 (95%CI: 0.52-2.95), $P = 0.005$, Figure 3]. In order to explore the source of heterogeneity, we performed a sensitivity analysis both by eliminating the study with the smaller sample size[26] and by removing from the analysis the low-quality study[22]. However, in both cases the results were in favor of a significantly shorter duration of the procedure in the EMR patients [standardized mean difference: 1.58 (0.12-3.03), $P = 0.03$ and 1.33 (0.52-2.14), $P = 0.001$, respectively] without obviating to the aforementioned heterogeneity ($P < 0.001$, $I^2 = 99\%$ and $P \leq 0.001$, $I^2 = 94\%$, respectively).

Eventual sources of publication bias were explored by means of visual examination of funnel plot (Figure 4) and of Begg and Mazumdar's test ($P = 0.03$). After editing funnel plot by trim and fill method, the standardized mean difference in operation time was smaller with the missing studies filled in, but the results still remained significant ($P = 0.04$).

En bloc resection rate

Eight studies reported the *en bloc* resection rate[8,21-23,25-28]. As no heterogeneity was found ($P = 0.15$, $I^2 = 34\%$), a fix model was performed (Figure 5). Overall *en bloc* resection rate resulted significantly higher in ESD patients [OR 9.69 (7.74-12.13), $P < 0.001$] with 1328 out of 1437 patients in ESD *vs* 1020/1973 in EMR group who underwent complete resection of the lesion. No publication bias was found ($P = 0.34$).

Histological complete resection rate

Nine studies reported histological resection rates[8,21-28]. A high grade of heterogeneity was found ($P < 0.001$, $I^2 = 92\%$), hence random model with inverse variance analysis was performed (Figure 6). ESD patients obtained a significantly higher histological resection rate [OR = 5.66 (2.92-10.96), $P < 0.001$]. In fact, 1227/1495 ESD patients and 867/2053 EMR patients reached this gold standard of endoscopic intervention.

Sensitivity examination of data was performed by

Table 1 Characteristics of included studies

Ref.	Country	Patients	Lesions	Article	Baseline consistency	Follow-up	End-points
Min *et al*[21] 2009	South Korea	ESD 243 EMR 203	ESD 243 EMR 203	Full text	No	29 (4-44) m	Operation time, *en bloc* resection rate, histologic curative resection rate, bleeding, perforation, recurrence
Oka *et al*[22]2006	Japan	ESD 185 EMR 711	ESD 195 EMR 825	Full text	No	ESD 19.4 ± 9.2 m EMR 83.2 ± 34.6 m	Operation time, *en bloc* resection rate, histologic curative resection rate, bleeding, perforation, recurrence
Oda *et al*[8]2006	Japan	655	ESD 303 EMR 411	Full text	No	39 (5-60) m	*En bloc* resection rate, histologic curative resection rate, perforation, recurrence (residual)
Catalano *et al*[23] 2009	Italy	45	ESD 12 EMR 36	Full text	Not Recorded	31 (12-71) m	Operation time, *en bloc* resection rate, histologic curative resection rate, bleeding, perforation, recurrence
Odashima *et al*[24] 2006	Japan	ESD 57 EMR 80	ESD 57 EMR 80	Abstract	Not Recorded	Not Recorded	Histologic curative resection rate
Hoteya *et al*[25] 2007	Japan	Not Recorded	ESD 304 EMR 350	Abstract	Not Recorded	Not Recorded	*En bloc* resection rate, histologic curative resection rate, delayed bleeding rate
Hoteya *et al*[26] 2010	Japan	Not Recorded	ESD 40 EMR 22	Full text	No	Not Recorded	Operation time, *en bloc* resection rate, histologic curative resection rate, perforation, recurrence
Nakamoto *et al*[27] 2009	Japan	ESD 106 EMR 71	ESD 122 EMR 80	Full text	Yes	54 (12-89) m	Operation time, *en bloc* resection rate, histologic curative resection rate, perforation, bleeding
Watanabe *et al*[28] 2010	Japan	ESD 219 EMR 146	ESD 219 EMR 146	Full text	Yes	ESD 14.3 m EMR 17.8 m	*En bloc* resection rate, histologic curative resection rate, perforation, recurrence
Tanabe *et al*[29] 2014	Japan	ESD 421 EMR 359	ESD 421 EMR 359	Full text	No	ESD 65 m EMR 73 m	Recurrence, overall survival

Follow up time (mo) is expressed as median (range) of mean (± SD) when appropriate. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection.

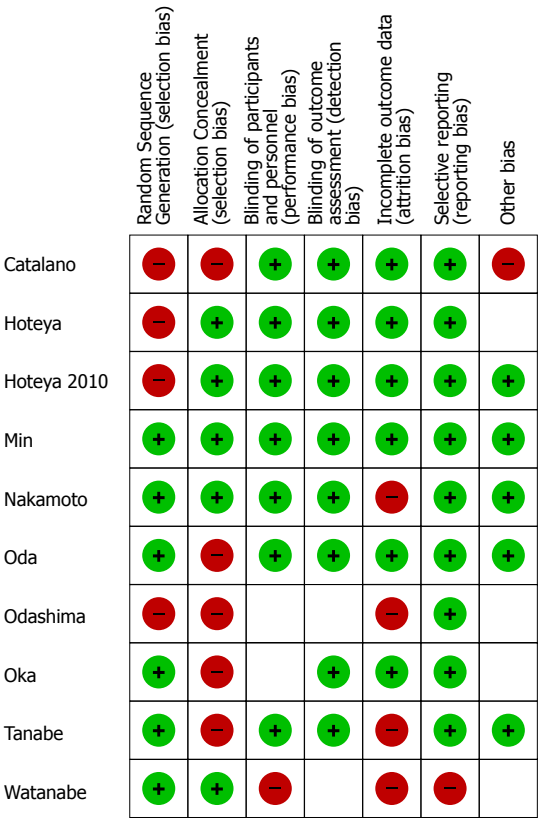

Figure 2 Quality of included studies according to the Cochrane Collaboration guidelines[7].

means of subgroup analysis, considering separately studies including only small EGCs (*i.e.*, < 10 mm)[21,22,27,28] and those based on greater lesions[8,23-26]. In both cases the better performances of ESD with respect to EMR resulted even amplified [OR = 9.28 (4.6-18.72), $P < 0.001$ and OR = 15.21 (11.2-19.98), $P < 0.001$, respectively]. A low grade of heterogeneity in the former studies and no heterogeneity at all in the latter was found ($P < 0.1$, $I^2 = 52\%$ and $P = 0.11$, $I^2 = 45\%$, respectively).

Evidence of publication bias was found ($P = 0.01$), hence trim and fill method was applied without losing the statistical significance of the rates previously reported ($P < 0.001$).

Recurrence rate

Data on local recurrence rate were reported in nine studies[8,21-23,25-29]. Recurrence rate resulted significantly lower after ESD [OR = 0.09 (0.05-0.17), $P < 0.001$] and low grade of heterogeneity was found ($P = 0.21$, $I^2 = 29\%$) (Figure 7). No evidence of publication bias was found ($P = 0.11$).

Perforation rate

Eight articles examined treatment-related perforation rate[8,21-23,25-28]. Perforations were significantly more common after ESD [OR = 4.67 (2.77-7.87), $P < 0.001$] (Figure 8). Further sensitivity analyses were not needed due to the low grade of heterogeneity ($P = 0.14$, $I^2 = 36\%$). Overall, 62/1438 cases of perforation after ESD and 17/1973 af-

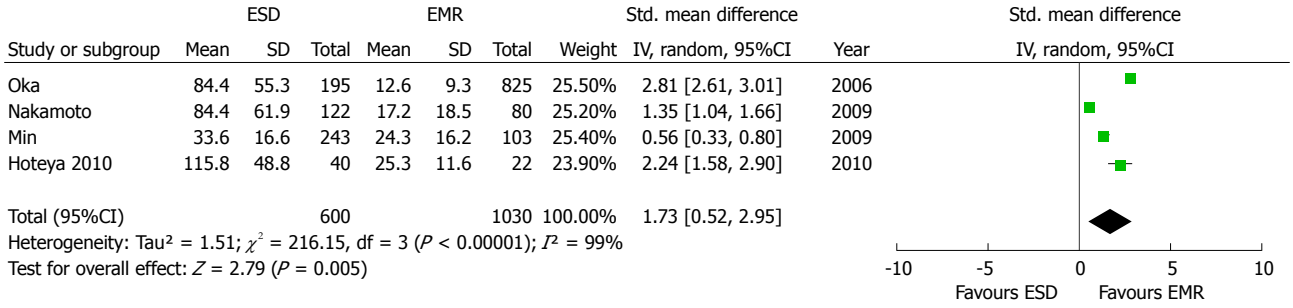

Figure 3 Forest plot of mean operation time. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; df: Degrees of freedom.

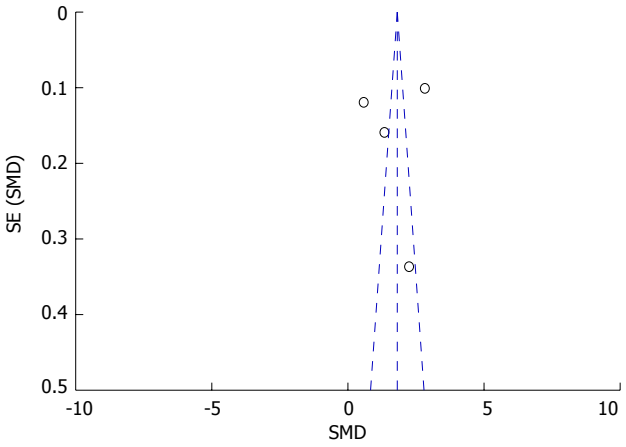

Figure 4 Funnel plot of publication bias for mean operation time.

ter EMR were reported. There was no evidence of publication bias ($P = 0.14$).

Bleeding rate

Five studies reported post-treatment bleeding rate[21-23,25,27]. As shown in Figure 9, bleeding rate was higher, although not significantly, after ESD [OR = 1.49 (0.6-3.71), $P = 0.39$]. Since high grade of heterogeneity was found ($P = 0.007$, $I^2 = 72\%$), a random effect model was built and sensitivity analyses were performed. In particular, restricting the analysis to the two studies reporting delayed bleeding rate after procedure[21,25], OR slightly decreased (1.04, 95%CI: 0.62-1.75) and no heterogeneity resulted. No evidence of publication bias was found ($P = 0.09$).

DISCUSSION

ESD represents a promising alternative to classical EMR for the treatment of EGCs. Two previous meta-analyses clearly demonstrated the superiority of ESD in terms of resection (both *en bloc* and histological) rate and recurrence rate with higher percentages of complications due to the complexity of the procedure[5,6]. Aim of this meta-analysis is to validate such results in light of the recently published studies on this topic.

A total of 10 studies analyzing the endoscopic treatment of 4328 lesions (1916 in the ESD and 2412 in the EMR group) were included in the current review. ESD was found to provide better outcomes in terms of lower recurrence rate and higher *en bloc* resection rate. As a consequence, ESD reached more frequently the complete histological removal of the treated lesions, which is the gold standard of each endoscopic interventional procedure. In this setting, the high OR [5.66 (2.92-10.96), $P < 0.001$] in favor of ESD stands for a clear superiority of such procedure for the treatment of non metastatic mucosal cancerous lesions of the stomach. The robustness of this finding was not affected from the high grade of heterogeneity because stratifying the analysis by the diameter of the lesions, no changes in the final outcomes were found. In fact, ESD resulted superior with respect to EMR in all the reviewed studies, regardless of the size of the treated lesions.

Unfortunately, broad and robust data on overall survival after endoscopic treatment of EGC are still too few for being included in a meta-analysis, hence this outcome could not be explored. However, the low aggressiveness and scarce attitude to extragastric spread of EGC should result in slight differences of survival outcomes between the two treatments. In fact, a recent study did not show significant differences in terms of overall survival between ESD and EMR despite lower recurrence rate after submucosal dissection[29].

Indubitably, ESD is a more complex procedure that should be performed in high-volume centers. Our meta-analysis confirms the results of previous systematic reviews finding higher procedure-related complication (both perforation and bleeding) rates and longer operation times in ESD patients. Among complications, particular concerns raise on regard to perforations. In fact our meta-analysis shows a significant association between ESD and perforation rate [OR = 4.67 (2.77-7.87), $P < 0.001$], thus meaning higher morbidity with respect to classical mucosal resection. Interestingly, bleeding rate showed only a non-significant trend in favor of EMR and restricting the analysis to delayed bleeding (the more insidious and difficult to treat), the two procedures resulted in similar rates (OR = 1.04, 95%CI: 0.62-1.75).

There are some limitations in our study. First, only retrospective non randomized studies are currently available in the literature, hence the absence of randomization may introduce patient selection biases. Second, the number of included studies is small. Third, estimation

Study or subgroup	ESD Events	ESD Total	EMR Events	EMR Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Oka	162	195	347	825	36.80%	6.76 [4.54, 10.08]	2006
Oda	281	303	230	411	23.20%	10.05 [6.25, 16.17]	2006
Hoteya	294	303	219	350	9.90%	19.54 [9.73, 39.26]	2007
Nakamoto	115	122	43	80	4.90%	14.14 [5.86, 34.10]	2009
Min	233	243	80	103	7.60%	6.70 [3.06, 14.68]	2009
Catalano	11	12	26	36	1.80%	4.23 [0.48, 37.17]	2009
Watanabe	194	219	66	146	14.80%	9.41 [5.54, 15.96]	2010
Hoteya 2010	38	40	9	22	1.00%	27.44 [5.24, 143.84]	2010
Total (95%CI)		1473		1973	100.00%	9.69 [7.74, 12.13]	
Total events	1328		1020				

Heterogeneity: χ^2 = 10.67 df = 7 (P = 0.15); I^2 = 34%

Test for overall effect: Z = 19.84 (P < 0.00001)

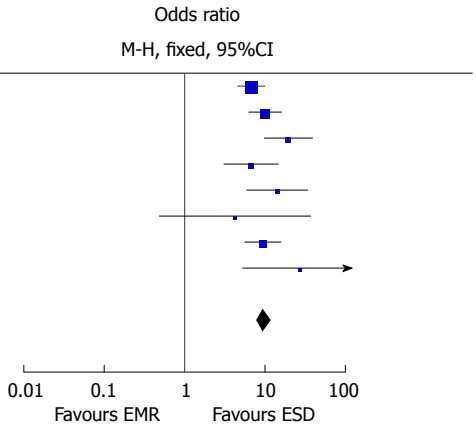

Figure 5 Forest plot of *en bloc* resection rate. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; M-H: Mantel-Haenszel; df: Degrees of freedom.

Study or subgroup	ESD Events	ESD Total	EMR Events	EMR Total	Weight	Odds ratio IV, random, 95%CI	Year
Oka	162	195	195	825	12.60%	15.86 [10.55, 23.83]	2006
Odashima	43	57	41	80	11.40%	2.92 [1.39, 6.16]	2006
Oda	223	303	251	411	12.90%	1.78 [1.29, 2.46]	2006
Hoteya	254	304	204	350	12.80%	3.64 [2.51, 5.26]	2007
Catalano	11	12	20	36	5.50%	8.80 [1.02, 75.55]	2009
Nakamoto	113	122	30	80	11.00%	20.93 [9.25, 47.32]	2009
Min	216	243	78	103	12.00%	2.56 [1.40, 4.68]	2009
Hoteya 2010	32	40	9	22	9.50%	5.78 [1.83, 18.25]	2010
Watanabe	173	219	39	146	12.40%	10.32 [6.32, 16.84]	2010
Total (95%CI)		1495		2053	100.00%	5.66 [2.92, 10.96]	
Total events	1227		867				

Heterogeneity: Tau^2 = 0.85; χ^2 = 99.48 df = 8 (P < 0.00001); I^2 = 92%

Test for overall effect: Z = 5.14 (P < 0.00001)

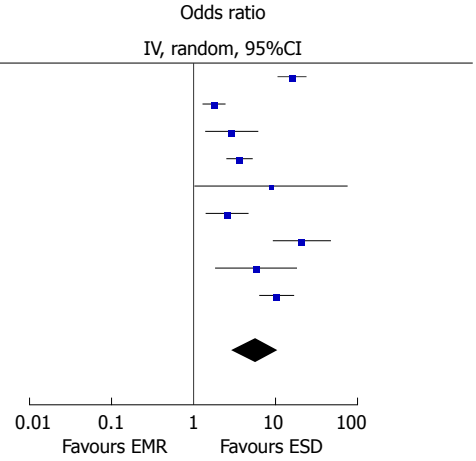

Figure 6 Forest plot of complete histologic resection rate. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; IV: Inverse variance; df: Degrees of freedom.

Study or subgroup	ESD Events	ESD Total	EMR Events	EMR Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Oka	0	195	31	825	9.30%	0.06 [0.00, 1.06]	2006
Oda	6	303	27	411	17.30%	0.29 [0.12, 0.70]	2006
Hoteya	0	304	13	350	9.70%	0.04 [0.00, 0.69]	2007
Nakamoto	0	122	14	80	13.40%	0.02 [0.00, 0.32]	2009
Min	0	243	0	103		Not estimable	2009
Catalano	0	12	0	36		Not estimable	2009
Watanabe	5	219	39	146	35.30%	0.06 [0.02, 0.17]	2010
Hoteya 2010	0	40	2	22	2.40%	0.10 [0.00, 2.21]	2010
Tanabe	1	421	15	359	12.50%	0.05 [0.01, 0.42]	2014
Total (95%CI)		1859		2332	100.00%	0.09 [0.05, 0.17]	
Total events	12		141				

Heterogeneity: χ^2 = 8.48 df = 6 (P = 0.21); I^2 = 29%

Test for overall effect: Z = 8.18 (P < 0.00001)

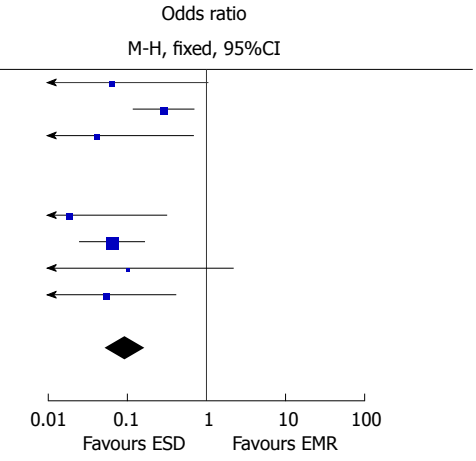

Figure 7 Forest plot of recurrence rate. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; M-H: Mantel-Haenszel; df: Degrees of freedom.

Figure 8 Forest plot of perforation rate. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; M-H: Mantel-Haenszel; df: Degrees of freedom.

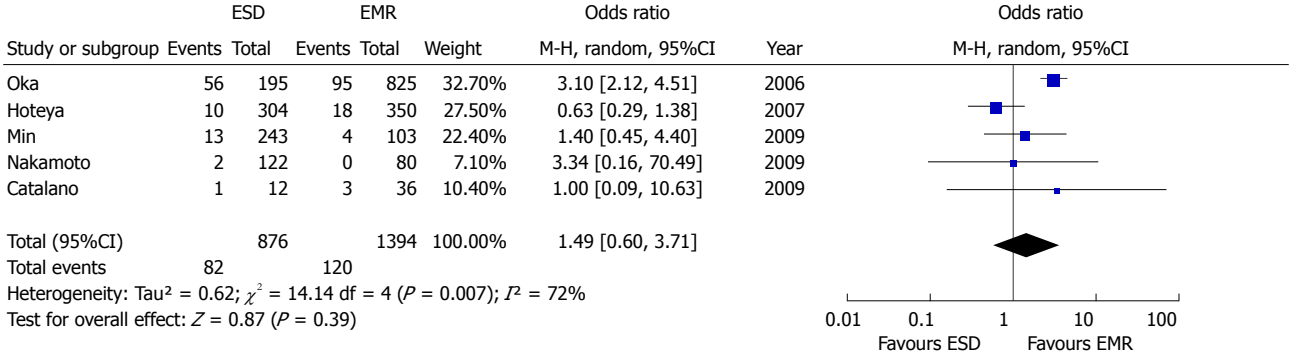

Figure 9 Forest plot of bleeding rate. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; M-H: Mantel-Haenszel; df: Degrees of freedom.

of overall survival was not feasible because of lack of long-term outcomes data in most of the studies included in the meta-analysis. Finally, only a low-quality, small Western study from Italy was included and most articles were from Eastern Asia, where high-experienced interventional endoscopists in high-volume centers deal with more EGC patients, hence the conclusions of the meta-analysis could be not applicable in Europe and United States.

Despite these limitations, our study has a number of strengths. It provides a comprehensive and simultaneous assessment of therapeutic efficacy, procedural complexity and safety profile of the two treatments. Second, any possible source of heterogeneity and publication bias that could have influenced the final results was explored by means of appropriate statistical tools and all the findings were confirmed performing sensitivity analysis.

In conclusion, ESD is a more effective therapy for EGC with higher *en bloc* and histologically complete resection rate and lower local recurrence in comparison to EMR, regardless of tumor size. On the other hand, its safety profile is affected from higher perforation rate which may limit its application in low-volume centers.

Broad randomized controlled trials from both Eastern and Western countries reporting also overall survival data are warranted in order to validate such findings.

COMMENTS

Background

Early gastric cancer (EGC) is a malignant tumor confined to the mucosa or the submucosa of the stomach regardless of lymph node metastases. Endoscopic submucosal dissection (ESD) was developed to overcome the problem caused by incomplete resection by conventional Endoscopic mucosal resection (EMR) for EGC. Aim of this meta-analysis is to compare the efficacy outcomes, expressed in terms of *en bloc* and histological complete resection rate and recurrence rate, and safety profile of ESD with respect to EMR for early gastric cancer.

Research frontiers

Most of the published literature in the field outlines the superior efficacy as well as the higher complication rate of ESD with respect to EMR.

Innovations and breakthroughs

This study provides an updated comprehensive comparison of therapeutic efficacy, procedural complexity and safety profile of the two treatments. Second, any possible source of heterogeneity and publication bias that could have influenced the final results was explored by means of appropriate statistical tools and all the findings were confirmed performing sensitivity analysis.

Applications

The results could be useful for endoscopists involved in gastric cancer management but they should be confirmed by large randomized controlled trials with long-term follow-up and should be validated both in Eastern and Western countries.

Terminology

EGC is a malignant tumor confined to the mucosa or the submucosa regardless of lymph node metastases. EMR has been proposed as a replacement for invasive surgery because of favorable long-term outcomes and improved quality of life for patients. EMR is widely accepted because of its minimal invasion, low

cost, patient tolerance and better quality of life after the operation. ESD was developed in the late 1990s to enable the *en bloc* removal of lesions larger than 2 cm.

Peer review

This study is a meta-analysis to compare the efficacy outcomes between ESD and EMR for early gastric cancer. The authors describe that ESD shows a superior complete resection rate but higher complication rate with respect to EMR. It has already well known that ESD provide the higher curability but higher complication rate compared to EMR. However, I believe this paper can give gastroenterologists useful information in treatments of early gastric cancer, as a review article of meta-analysis of previously published data.

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CASE REPORT

Symptomatic pneumatosis intestinalis (including portal venous gas) after laparoscopic total colectomy

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Author contributions: All authors have made a substantial contribution to conception and design of this study and also to the acquisition and analysis and interpretation of data; all were involved in the article drafting and critical revision for important intellectual content and the final approval of the version to be published.

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Abstract

The development of intramural intestinal gas may indicate a serious postoperative complication and therefore any radiological indication of such "pneumatosis intestinalis" (PI) in an unwell patient after surgery should put the clinical team on high-alert. However immediate recourse to relook laparotomy may not be always necessary and, further, in some cases may possibly accelerate the deterioration especially if it proves to be non-therapeutic. Careful and close clinical monitoring, as is described in this clinical report, may allow discriminative identification of those in whom this finding is in fact transient and therefore benign and who therefore can be successfully treated without operative re-intervention. We describe the presenting features and background scenario of PI early after laparoscopic total colectomy for medically refractory, severe ulcerative colitis and detail the critical postoperative decision pivots.

Key words: Pneumatosis intestinalis; Laparoscopic total colectomy; Ulcerative colitis; Severe acute colitis; Portal venous gas

Core tip: The successful outcome of our patients with postoperative pneumatosis intestinalis (PI) indicates that a very individualized, nuanced management plan can allow a succesful course with conservative management. At all times it should be remembered that PI developing postoperatively is a radiographic sign rather than a specific diagnosis. It should be a factor in the decision-analysis related to clinical care and not the sole arbitrator.

Shah A, Al Furajii H, Cahill RA. Symptomatic pneumatosis intestinalis (including portal venous gas) after laparoscopic total colectomy. *World J Gastrointest Endosc* 2014; 6(11): 564-567 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i11/564.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i11.564

INTRODUCTION

"Pneumatosis intestinalis" (PI) is the presence of extraluminal gas within the bowel wall[1]. In a symptomatic postoperative patient such a finding on plain radiology or computerized tomography (CT) is often viewed as a signal of impending or actual acute mesenteric ischaemia especially when associated with portal venous gas (PVG)[2]. Therefore many advocate immediate exploratory laparotomy due to associated high mortality rates. Here, we present two patients who developed PI (one with PVG) in association with abdominal pain and clinical signs early after laparoscopic total colectomy for acute severe ulcerative colitis but who were managed conservatively with prompt complete recovery.

CASE REPORT

Case one

A 22-year-old male known to have medically (steroid and biologic therapy) refractory ulcerative colitis (UC) was

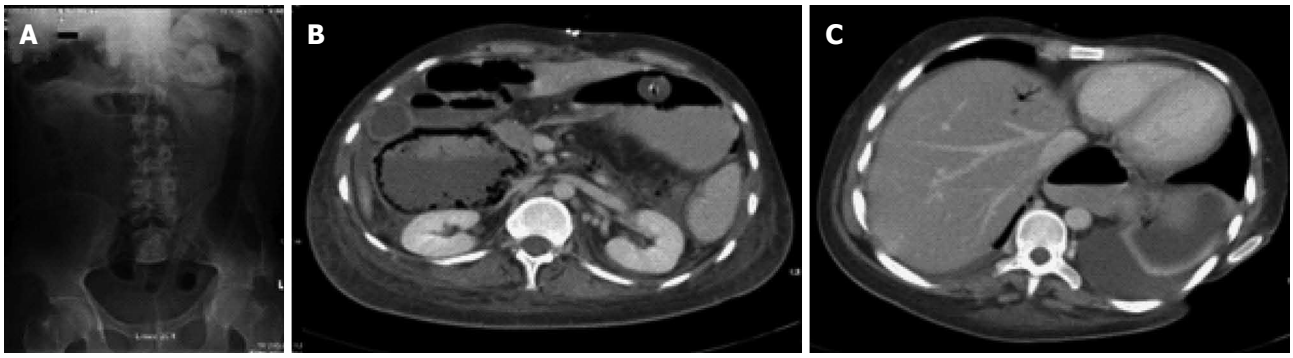

Figure 1 Radiology of case one. (A) Preoperative plain film of abdomen showing no pneumatosis intestinalis in comparison to (B) postoperative computerized tomogram showing extensive intramural gas and (C) portal venous gas.

admitted with an acute exacerbation (10-15 bloody bowel movements daily for the previous 8 d). Interestingly, he had also micrognathia with several prior jaw reconstruction procedures and had both a tracheostomy and gastrostomy feeding tube. Laboratory investigations on admission showed leucocytosis [white blood cell (WBC) count = 12.29 × 10^{-9}/L] and an elevated C-reactive protein (CRP) level of 27 mg/L and normal haemoglobin (Hb, 13.8 g/dL) and albumin (32 g/L) levels. Plain abdominal X-ray on admission showed a loss of tone and haustra of the descending and sigmoid colon (Figure 1) but no megacolon. He underwent urgent multiport laparoscopic total colectomy with end ileostomy formation without intra-operative complication within the first 48 h of admission.

While our patient was well for the first 24 h postoperatively (including stoma function), he then developed generalized abdominal pain associated with absence of stoma function, pallor, tachycardia (120 beats per minute) and hypotension (90/60 mmHg). On examination, his abdomen was soft without tenderness to palpation. An urgent CT scan of his abdomen with intravenous and oral contrast showed dilated small bowel loops with PI, associated gas within the portal venous system and a right-sided portal venous thrombus (also Figure 1). Clinical examination was unchanged after the scan and the patient symptomatically was improved. We therefore opted to closely observe and support him medically (including commencement of Total Parenteral Nutrition (TPN) and empiric antibiotic therapy to cover any possible bacterial translocation) along with therapeutic low molecular weight heparin anticoagulation. Over the next 24 h his symptoms settled fully and his ileostomy resumed functioning. He was discharged home 9 d later on oral anticoagulation. At review 3 mo post-operatively, he was well with a repeat CT abdomen showing significant interval resolution of his PI and PVG. The portal vein thrombus was still present but non- occlusive. He remains well now 18 mo after his surgery.

Case two

A 33-year-old woman presented acutely with an acute exacerbation of her known UC despite prior steroid and infliximab therapy. Her WCC and CRP levels were elevated (12.29 × 10^{-9}/L and 57 mg/L respectively) and she was both anaemic (10.7 g/dL) and hypoalbuminemia (27 g/L). She underwent single port laparoscopic total colectomy with end ileostomy on an urgent basis and convalesced normally for the first three postoperative days. She then developed abdominal pain and tachycardia but without abdominal tenderness. An urgent CT scan showed PI (Figure 2) but no portal venous gas. Again her symptoms and signs showed no progression and she settled with active, careful observation in addition to assiduous rehydration and empiric antibiotic therapy. Although she was discharged home on day 8 postoperatively, she was readmitted with fever and abdominal pain secondary to an intra-abdominal abscess (seen on repeat CT without any associated PI) that was drained radiologically. She made an excellent recovery thereafter and thereafter underwent laparoscopic proctectomy with ileoanal J-pouch construction twelve months after her colectomy. She is now six months post-reversal of her defunctioning loop ileostomy and her quality of life and pouch function are both excellent.

DISCUSSION

Much prior experience has indicated that the finding of PI (most especially in association with PVG[3]) on post-operative imaging in an unwell patient is an ominous sign that should trigger re-exploratory surgery, likely laparotomy[4,5]. However, in other settings, PI is known to have a benign course and the same appearances can be seen in association with steroid or chemotherapy usage, trauma and inflammatory conditions[6]. Furthermore, there have been reports of resolution of PI with hyperbaric oxygen therapy[7]. The clinical spectrum of PI in this way is therefore already known to range from asymptomatic to life threatening course[8]. While surgery is of course necessary in situations of bowel strangulation, frank gangrene or perforation, injudicious take-back may be non-therapeutic (the affected loop of bowel may not even be macroscopically abnormal) and in fact risk precipitating promulgation of the underlying inflammatory/thrombotic cascade mitigating towards poor outcome. While increasing use of

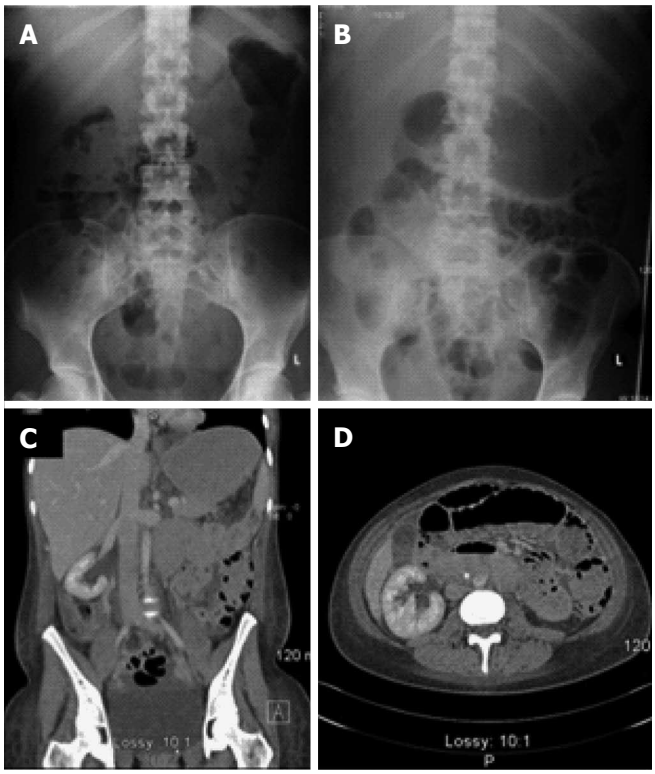

Figure 2 Radiology of case two. (A) and (B) comparative pre and postoperative plain radiology showing new and extensive intramural gas in the latter; C and D: Axial computerized tomograms taken on the 8th postoperative day showing marked pneumatosis intestinalis.

CT imaging has led to quicker and earlier detection[9], the increasing sophistication of this modality includes greater sensitivity for non-critical findings. Management decisions should therefore be based on a combination of both radiological and laboratory findings[10] but clinical examination (repeated frequently) and judgment is paramount.

While the PI identified in both patients in this report was shown to be transient (it had resolved completely on follow-up imaging) potentially it was present prior to the operative procedure (neither had preoperative CT imaging). Certainly too the portal venous thrombosis seen in case one may have been present preoperatively as both it and PI share as risk factors many of the concomitants associated with acute colitis (namely dehydration, systemic inflammatory syndrome, immobility, steroid therapy). Colitic patients may also have an increased hereditary tendency to thrombosis[11]. Nonetheless positive intra-abdominal pressure at laparoscopy may certainly have had an additive effect and it seems more likely that the operation indeed triggered the clinical course and radiological findings.

Experiential reports on postoperative PI in symptomatic patients remain very limited. Until there is greater data on the specific incidence and an improved understanding aetiology on the conservative management of such patients, we agree that a radiological indicator of PI should put the clinical team on high-alert. However the successful outcome of our patients with a conservative course in conjunction with poor outcomes occasionally seen in those undergoing early operative intervention indicates that a very individualized, nuanced management plan is then required in order to ensure therapeutic opportunities are maximized.

COMMENTS

Case characteristics

Two unwell patients with pneumatosis intestinalis found on radiological examination early after laparoscopic total colectomy for acute severe and medically refractory colitis.

Clinical diagnosis

Acute deterioration early after surgery indicating radiological investigation that showed intramural intestinal gas or "pneumatosis intestinalis" as a new finding.

Differential diagnosis

Ischaemic bowel secondary to a strangulated internal hernia, intra abdominal abscess, ileus with pneumatosis as a transient, benign co-finding.

Laboratory diagnosis

Acute inflammatory response syndrome.

Imaging diagnosis

Pneumatosis intestinalis (including one patient with portal venous gas) very concerning for grave intra-abdominal complication.

Pathological diagnosis

Benign, self-limiting complication that settled with intensive clinical observation without the need for operative re-intervention.

Treatment

Close clinical observation along with rehydration, bowel rest, analgesia and antibiotic therapy.

Related reports

Very often the concern that pneumatosis intestinalis represents ischaemic bowel means that some authors advocate immediate laparotomy even though some have then found essentially normal intraperitoneal appearances and the patients clinical deterioration continues thereafter.

Term explanation

Pneumatosis intestinalis-the presence of intramural gas within the intestine.

Experience and lessons

Careful clinical care and consideration can allow successful management without operative re-intervention of this very worrying radiological finding.

Peer review

Two interesting cases regarding symptomatic pneumatosis intestinalis post laparoscopic surgery.

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CASE REPORT

Early endoscopic retrograde cholangiopancreatography after laparoscopic cholecystectomy can strain the occurrence of trocar site hernia

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Abstract

This study reports a 69-year-old, obese, female patient presenting with a biliary leakage after laparoscopic cholecystectomy for cholelithiasis. Closure of the umbilical trocar site had been neglected during the laparoscopic cholecystectomy. Early, on postoperative day five, endoscopic retrograde cholangiopancreatography (ERCP) requirement after laparoscopic cholecystectomy resolved the biliary leakage problem but resulted with a more complicated clinical picture with an intestinal obstruction and severe abdominal pain. Computed tomography revealed a strangulated hernia from the umbilical trocar site. Increased abdominal pressure during ERCP had strained the weak umbilical trocar site. Emergency surgical intervention through the umbilicus revealed an ischemic small bowel segment which was treated with resection and anastomosis. This report demonstrates that negligence of trocar site closure can result in very early herniation, particularly if an endoscopic intervention is required in the early postoperative period.

Key words: Laparoscopic cholecystectomy; Trocar site hernia; Endoscopic retrograde cholangiopancreatography; Postoperative complications

Core tip: This report demonstrates that negligence of trocar site closure after laparoscopic surgery can result in very early trocar site herniation. This may occur particularly if an endoscopic intervention is required in the early postoperative period. Suturing the trocar site is not only important for the late trocar site herniations, it is imperative for early hernia problems as well.

Sumer F, Kayaalp C, Yagci MA, Otan E, Kocaaslan H. Early endoscopic retrograde cholangiopancreatography after laparoscopic cholecystectomy can strain the occurrence of trocar site hernia. *World J Gastrointest Endosc* 2014; 6(11): 568-570 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i11/568.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i11.568

INTRODUCTION

Progress in minimally invasive procedures such as endoscopy or laparoscopy has resulted in revolutionary changes in clinical practice. Gastrointestinal endoscopy, particularly interventional procedures, have replaced some complicated surgical methods and improved patient care. On the other hand, the use of laparoscopy is increasing in most of the gastrointestinal surgical procedures. However, these minimal invasive procedures have themselves developed some very specific complications, particularly when they are combined. This study presents a case of strangulated perforated Richter's hernia from the umbilical trocar site following laparoscopic cholecystectomy in the early postoperative period. This complication was

accelerated by the requirement of early endoscopic retrograde cholangiopancreatography (ERCP) for the postoperative biliary leakage.

CASE REPORT

A 69-year-old female patient with a body mass index of 32 kg/m^2 underwent laparoscopic cholecystectomy for cholelithiasis in a rural district hospital. On postoperative day one, abdominal drainage was 200 cc/d with bile content. The patient was referred to our center for diagnosis and treatment of the biliary leakage. The primary surgeon of the patient informed us that he identified the intact common bile duct during surgery but the procedure was difficult due to the inflammation of the gall bladder. Physical examination revealed no findings of peritonitis or evident abdominal distention. The laparoscopic cholecystectomy had been performed by conventional four trocars (two 11 mm and two 5 mm). Laboratory test results were within normal ranges. Abdominal ultrasound displayed a collection only 4 cm in diameter in the gall bladder bed. Because of the ongoing biliary leakage, an ERCP was performed on the 5th postoperative day. ERCP revealed a leakage from the cystic stump and a biliary 7F stent was placed. The procedure was completed uneventfully and the next day of ERCP the biliary leakage decreased immediately. However, an abrupt abdominal distention, pain and vomiting occurred after the ERCP procedure. Abdominal examination displayed tenderness, especially around the umbilicus. Obesity and previous surgery did not allow an objective examination of the umbilicus. Abdominal X-ray revealed air-fluid levels (Figure 1). Post-ERCP amylase value was 87 U/L (normal range: 36-128). Repeated abdominal ultrasound examinations showed that the previous collection at the gall bladder bed had disappeared. Her laboratory results were within normal limits during the two-day follow-up, but her symptoms (pain, vomiting and distention) persisted. Finally, a computed tomography on postoperative day 7, revealed the herniated intestine inside the umbilical trocar site (Figure 2). The patient underwent an emergency surgical treatment under general anesthesia. A laparotomy was performed containing the umbilical trocar site incision and an ileal anti-mesenteric loop was observed to be herniated. There was no previous fascia suturing at the umbilical trocar site. A small ileal segment of 3-4 cm in length was ischemic which consisted of a millimetric perforation. The rest of the abdominal exploration findings were normal. Following resection of the ischemic perforated ileal segment, a side-to-side intestinal anastomosis was performed. Postoperative course was uneventful and the patient was discharged on day eight of the second surgery.

DISCUSSION

The incidence of trocar site hernias in systematic reviews are generally reported as 1.7% (ranged 0.65%-2.80% or 0.3%-5.4%)[1,2], some studies reported a quite high incidence as 25.9%[3]. If we ignore the fact its incidence,

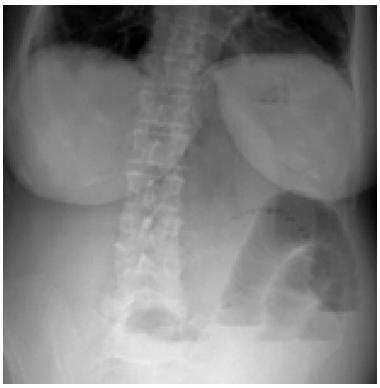

Figure 1 Plane abdominal X-ray demonstrated the findings of intestinal obstruction. The small bowel segment was dilated and there were air-fluid levels.

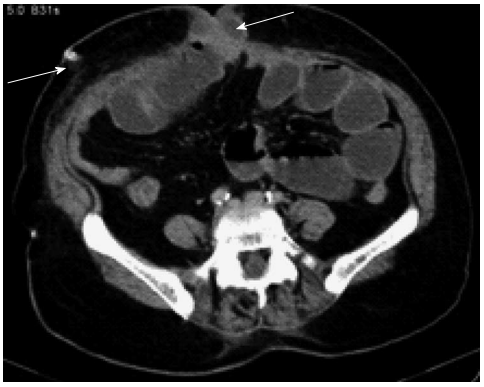

Figure 2 Incarcerated intestinal loops in the umbilical trocar site. Arrows point out the abdominal drain and the incarcerated intestinal loops through the umbilicus.

they have the potential to cause serious complications[4]. Predisposing factors are using larger size trocars, leaving fascial defects open, midline positioned trocar sites, stretching the port sites for retrieving specimens, obesity, malnutrition, older age and surgical site infections[4]. Time period between the previous surgery and the diagnosis of trocar site hernia varies but reported as a mean 9.2 mo (ranged from 5 d to 3 years)[2]. In the very early postoperative period, they occur rarely and cause confusion in diagnosis if particularly accompanied with intestinal obstruction, strangulation or perforation. Diagnosis of hernia can be significantly difficult in obese patients. Infection and hematoma in the surgical site may also contribute to the under-diagnosis. Additionally, a co-existing intra-abdominal complication, which was a biliary leakage in our case, may lead to overlooking this relatively rare condition. Abdominal distention and pain can be considered to be related to the complications of the ERCP itself. Differential diagnosis needs careful clinical evaluation and radiological examinations.

Trocar site hernia after laparoscopic cholecystectomy usually include omentum or small bowel. In cases with presence of omentum in the sac, abdominal pain is generally mild[2]. Trocar site hernias following laparoscopic cholecystectomy are usually Richter hernias without stran-

gulation, however, they rarely result in obstruction or perforation[2]. Computed tomography has several advantages for the evaluation of the abdominal wall over the other radiological methods, particularly in the patients with a high body mass index, mild clinical symptoms, hematoma or infection in the surgical site. Computed tomography is also beneficial for the differential diagnosis of the other postoperative complications. Persistent complaints and obscure physical examination findings confused us when making the diagnosis, but computed tomography revealed the umbilical trocar site hernia exactly.

Development of strangulation following upper gastrointestinal endoscopy or colonoscopy was reported in already known umbilical, diaphragmatic or Spigelian hernias[5]. However, there was no previous report considering the predisposing effect of endoscopic procedures (gastroscopy, colonoscopy or ERCP) during the early postoperative period on the development of trocar site herniation. The unknown hernia was diagnosed after the endoscopic procedure even though it had developed into a strangulated hernia. Early postoperative ERCP by increasing the intra-abdominal pressure promoted the trocar site hernia when the fascial defect was left open.

It was reported that following laparoscopic surgical procedures, 86.3% of the trocar site hernias were from incisions where trocars greater than 10 mm were used[6]. Although all the trocar defects greater than 10 mm should be closed as a rule, trocar site closures can sometimes be neglected with obese patients or after prolonged, difficult, devastating laparoscopic procedures. It is most likely for this reason that the primary surgeon of this case did not close the umbilical trocar site. Closure of trocar site fascial defects avoid trocar site hernias in the long-term follow-ups, however, they should be closed for the prevention of very early postoperative hernia complications.

As a conclusion, postoperative early endoscopic procedures may aggravate development of early herniation from trocar sites when fascial defects are left open.

COMMENTS

Case characteristics

The patient was referred to our center for diagnosis and treatment of the biliary leakage after laparoscopic cholecystectomy and a biliary 7F stent was placed by endoscopic retrograde cholangiopancreatography (ERCP) on the 5th postoperative day.

Clinical diagnosis

An abrupt abdominal distention, pain and vomiting occurred after the ERCP procedure.

Differential diagnosis

Abdominal X-ray revealed air-fluid levels.

Laboratory diagnosis

Post-ERCP amylase value was 87 U/L (normal range: 36-128).

Imaging diagnosis

Computed tomography on postoperative day 7, revealed the herniated intestine inside the umbilical trocar site. The patient underwent laparotomy for the diagnosis of umbilical trocar site herniation of the ileal anti-mesenteric loop. There was no previous fascia suturing at the umbilical trocar site.

Pathological diagnosis

A ileal segment of 3-4 cm in length was ischemic which consisted of a millimetric perforation.

Treatment

Ischemic perforated ileal segment was resected.

Related reports

There was no previous report considering the predisposing effect of endoscopic procedures (gastroscopy, colonoscopy or ERCP) during the early postoperative period on the development of trocar site herniation.

Experiences and lessons

Suturing the trocar site is not only important for the late trocar site herniations, it is imperative for early hernia problems as well.

Peer review

This case is interesting and relatively low in incidence.

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REVIEW

Quality indicators for colonoscopy: Current insights and caveats

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Abstract

Colonoscopy is the diagnostic modality of choice for investigation of symptoms suspected to be related to the colon and for the detection of polyps and colorectal cancer (CRC). Colonoscopy with removal of detected polyps has been shown to reduce the incidence and mortality of subsequent CRC. In many countries, population screening programs for CRC have been initiated, either by selection of patients for colonoscopy with fecal occult blood testing or by offering colonoscopy directly to average-risk individuals. Several endoscopy societies have formulated quality indicators for colonoscopy. These quality indicators are almost always incorporated as process indicators, rather than outcome measures. This review focuses on the quality indicators bowel preparation, cecal intubation rate, withdrawal time, adenoma detection rate, patient comfort, sedation and complication rate, and discusses the scientific evidence supporting them, as well as their potential shortcomings and issues that need to be addressed. For instance, there is still no clear and generally accepted definition of adequate bowel preparation, no robust scientific evidence is available supporting a cecal intubation rate ⩾ 90% and the association between withdrawal time and occurrence of interval cancers has not been clarified. Adenoma detection rate is currently the only quality indicator that has been shown to be associated with interval colorectal cancer, but as an indicator it does not differentiate between subjects with one or more adenoma detected.

Key words: Colonoscopy; Quality indicators; Bowel preparation; Cecal intubation; Withdrawal time; Adenoma detection rate; Screening; Complication; Interval colorectal cancer; Post-colonoscopy colorectal cancer

Core tip: Many endoscopy societies have formulated guidelines on quality indicators for colonoscopy, including bowel preparation, cecal intubation rate, withdrawal time and adenoma detection rate. These are mostly consensus-based process indicators, rather than outcome measures. The scientific evidence on which they are based is limited. Adenoma detection rate is currently the only quality indicator that has been shown to be directly associated with interval colorectal cancer, but also has its shortcomings.

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INTRODUCTION

Colonoscopy is the diagnostic modality of choice for investigation of symptoms suspected to be related to

the colon and for the detection of polyps and colorectal cancer (CRC). Colonoscopy with polypectomy has been shown to reduce both the incidence and mortality of subsequent CRC[1,2].

However, despite being the gold standard, colonoscopy is also known to be not a perfect test. From back-to-back colonoscopy studies, it is estimated that up to 25% of polyps are missed during colonoscopy[3,4]. Furthermore, the preventive effect of colonoscopy is most prominent for distal CRCs, whereas its role in preventing proximal CRCs is less evident[5,6]. Finally, up to 8% of CRCs occur within 3 years after a previous colonoscopy[7-12]. Despite technical advancements and increased professional awareness, this miss rate has not decreased over time[12]. Moreover, recent studies have shown that these so-called post-colonoscopy CRCs are most likely due to missed lesions, rather than being completely new lesions[13,14].

The incidence of CRC is steadily rising in many parts of the world[15]. Many countries have initiated population screening programs for CRC, either through selection of patients for colonoscopy with fecal occult blood testing (FOBT) or by offering colonoscopy directly to average-risk individuals[16,17]. This has resulted in an increase in the number of colonoscopies performed. For these mass screening programs to be successful, it is of utmost importance that colonoscopies are of high quality and performed according to the latest state of knowledge.

In an effort to optimize general performance of colonoscopy and to decrease inter-individual variation between physicians performing colonoscopy, several quality indicators have been suggested in recent years[18]. These quality indicators however all are process indicators rather than indicators of outcome. Ideally, the quality of colonoscopy should be measured by clinical outcome measures. The goal of colonoscopy in most cases is the detection of neoplastic lesions. After removal of premalignant neoplastic lesions, patients enter a surveillance program. The rate of the occurrence of interval cancers or post-colonoscopy CRCs, defined as CRCs diagnosed in the period between the last colonoscopy and the scheduled surveillance colonoscopy, is a more direct and probably better reflection of the quality of the colonoscopy performed than the main current quality indicators proposed in guidelines.

In this review, we will discuss the main current quality indicators for colonoscopy, the scientific evidence supporting them, as well as their potential shortcomings and issues that still need to be addressed.

BOWEL PREPARATION

A quality indicator issued by several international guidelines is that the endoscopist should report the quality of the bowel preparation for each colonoscopy[18,19]. Several guidelines state that ≥ 90% of patients undergoing colonoscopy should have had a bowel preparation rated as excellent or at least adequate[19,20]. The quality of bowel cleansing has been shown to impact the ability and time needed to reach the cecum and the detection of polyps, both small and large (≥ 10 mm)[21,22].

There are several bowel preparation medications available and regimens used for bowel preparation before colonoscopy. These vary from polyethylene glycol (PEG) based solutions, osmotic laxatives (sodium phosphate, magnesium citrate, sodium sulphate) or stimulant laxatives (senna, bisacodyl, sodium picosulphate), either alone or in combination.

In a meta-analysis of randomized controlled trials, split dose bowel preparation before colonoscopy has been demonstrated to significantly improve the number of satisfactory bowel preparations, and is associated with increased patient compliance and decreased nausea compared with full-dose PEG[23]. In a systematic review and meta-analysis, Enestvedt *et al*[24] concluded that bowel preparation with 4 liter of split dose PEG-solution is superior than other bowel preparation methods. Several endoscopy societies now recommend 4 liter split dose PEG-solution as the first choice bowel preparation[25], although 2 liter PEG-solution with ascorbate may be an alternative in the non-constipated patient. Routine use of sodium phosphate preparations is not recommended because of safety concerns, especially in patients with renal insufficiency[25]. In patients using PEG-solutions, the interval between the last ingested dose of PEG-solution and the colonoscopy should be 3-5 h, as this has been shown to result in significantly better bowel preparation[26,27].

In the literature, several risk factors for inadequate bowel preparation have been identified. Increasing age[28-31] and male gender[29-32] have repeatedly been reported. A medical history of colorectal surgery[28,29], diabetes[28,29] and cirrhosis[29,32], as well as inpatient status[30,32] have also been identified as risk factors for inadequate bowel preparation in several studies. Other risk factors that have been suggested in the literature are a procedural indication of constipation, a reported failure to successfully complete the bowel lavage, the use of tricyclic antidepressants, a history of stroke or dementia[32], a history of Parkinson's disease, being overweight, having had a positive FOBT[29], a history of hysterectomy[28] and being of African-American descent[31]. A history of previous polypectomy was a negative predictive factor for inadequate bowel preparation in the study by Ness *et al*[32]. Furthermore, a later colonoscopy starting time during the day[30-32] was associated with inadequate bowel preparation in several studies. Most of these studies however were conducted before the wide application of a split-dose bowel preparation regimen. Whether this association currently still is valid remains to be elucidated.

Several scales have been developed to standardize the reporting of bowel preparation quality. Aronchick *et al*[33] were the first to propose a validated bowel preparation scale. This is a 5 point categorical scale, rating bowel preparation as excellent (small volume of clear liquid; >

95% of surface seen), good (large volume of clear liquid covering 5%-25% of surface; > 90% of surface see), fair (some semi-solid stool suctioned or washed away; > 90% of surface seen), poor (semi-solid stool that could not be suctioned or washed away; < 90% of surface seen) or inadequate (repeat bowel preparation necessary). Unfortunately, the reliability of this scale for the distal colon is rather poor.

Rostom and Jolicoeur developed and prospectively validated another bowel preparation scale, the Ottawa scale[34]. In this scale, the colon is divided into three segments: right colon (cecum and ascending colon), mid colon (transverse and descending colon) and rectosigmoid. For each segment, bowel preparation is qualified using a 4 point scale (0: perfectly clear to 4: solid stools and lots of fluid) for each colon segment individually and a 0 to 2 fluid quantity rating as a global value for the entire colon. The scale thus has a range from 0 (perfect bowel preparation) to 14 (completely unprepared).

Finally, in 2009 Lai *et al*[35] introduced the Boston Bowel Preparation Scale (BBPS). In this validated bowel preparation scale, the colon is divided into the right colon (cecum and ascending colon), transverse colon (including both the hepatic and splenic flexure) and the left colon (descending colon and rectosigmoid). The BBPS is a ten point scale (0-9) with 0-3 points allocated to each colon segment, *i.e.,* 0 (unprepared colon segment that cannot be cleared), 1 (portion of mucosa of the colon segment seen, but other areas of the colon segment not well seen due to staining, residual stool and/or opaque liquid), 2 (minor residual staining, small fragments of stool and/or opaque liquid, but mucosa of colon segment seen well) 3 (entire mucosa of colon segment seen well with no residual staining, small fragments of stool or opaque liquid). In the validation study, a score of $\geqslant 5$ was considered adequate.The BBPS differs from other preparation scales in that the score is applied after the endoscopist has performed cleansing maneuvers, like suctioning and washing.

All these scales have mainly been used in studies comparing new formulas or different schemes for bowel preparation[33,36-40], rather than being used to assist in clinical decision making. In a recent retrospective study, Calderwood *et al*[41] reported that the BBPS correlated with endoscopist behavior with regard to the advice for follow-up intervals for colonoscopy. A total BBPS score of $\geqslant 6$ and/or all segment scores $\geqslant 2$ provided a standardized definition of an "adequate" bowel preparation, whereas in 96% of examinations with a total score of $\leqslant 2$ a repeat examination within 1 year was recommended. For scores 3 to 5 however, recommended surveillance intervals varied widely between endoscopists. Future studies should focus on prospectively evaluating these cut-offs for surveillance interval recommendations and ideally associating them with relevant clinical outcome measures.

The widely adopted quality indicator for bowel preparation has several shortcomings. First of all, there is still no clear and generally accepted definition of adequate bowel preparation. Furthermore, the mere reporting of the quality of bowel preparation in itself is unlikely to significantly affect the quality of the colonoscopies performed, unless it becomes more clear what bowel preparation quality is the absolute minimum to detect relevant findings and to prevent interval cancers. There is also no clear policy on how to proceed when a patient's bowel is inadequately cleansed; the only relevant published studies on this topic had either small patient numbers[42] or a retrospective design[43].

The rule that $\geqslant 90\%$ of patients undergoing colonoscopy should have an excellent or adequate bowel preparation is consensus based and has found its way into several guidelines[19,20]. However, there is no scientific evidence to support this cut-off at 90%. Although inadequate bowel preparation has been shown to negatively affect the rate of detected polyps, this does not appear to be the case for CRCs[21]. It is conceivable that, through the negative effect on the detection of adenomas, an inadequate bowel preparation is associated with a higher rate of interval cancers, but to date, there is no direct evidence to support this.

CECAL INTUBATION RATE

In order to visualize the entire colonic mucosa, intubation of the endoscope to the cecum is mandatory. Cecal intubation is defined as introduction of tip of the colonoscope into the cecal pole, proximal of the ileocecal valve in order to have the entire cecum visualized. Although this sometimes may be challenging, there is consensus that each endoscopist should have a cecal intubation rate of $\geqslant 90\%$ of all cases[18-20,44,45]. When not taking into account obstructing CRCs, inadequate bowel preparation or severe colitis, this adjusted cecal intubation rate should be $\geqslant 95\%$[18]. Also, in $\geqslant 95\%$ of all screening colonoscopies the cecum should be intubated[18,19]. Furthermore, cecal intubation should be documented by naming and photographing the landmarks of the cecum, *i.e.,* the appendiceal orifice, the ileocecal valve and/or the terminal ileum.

In the literature, several factors have been associated with a higher risk of incomplete colonoscopy or more difficult intubation, with female gender being the most frequently reported predictive factor[46-50]. In addition, patients with advanced age[46,49,50] or a low body mass index[48-50], or in women with a history of hysterectomy[47] or diverticular disease[50], colonoscopy is reported to be more difficult and more often incomplete. Finally, poor bowel preparation and lower endoscopist annual case volume have been reported to be associated with a higher risk of incomplete colonoscopy[49].

Completeness of the colonoscopy is associated with a reduction in mortality from CRC[6]. In a study by Neerincx *et al*[51], a secondary colonoscopy after previous incomplete colonoscopy yielded initially missed advanced

neoplasia (CRC or advanced adenoma) in 4.3% of patients. In a study on the yield of CT-colonography after incomplete colonoscopy in 136 patients, in 13.9% of patients one or more additional colonic neoplastic lesions (polyp(s) and/or CRC) were found[52].

These findings suggest that in cases of incomplete colonoscopy the clinician should always perform additional imaging to visualize the remaining colon. Following incomplete colonoscopy, the cecum can usually be intubated in the majority of patients during a repeat colonoscopy with readily available endoscopic instruments, suggesting that a repeat colonoscopy should always be considered[47,53]. CT-colonography might be a useful alternative in these cases, with the additional benefit of detecting potentially relevant extra-colonic findings[52].

It is important to keep in mind that there is no robust scientific evidence for a cecal intubation rate of $\geqslant$ 90%. Although it is obvious that an endoscopist is not able to adequately inspect colon segments that were not intubated, the accepted minimal cecal intubation rate is based on consensus rather than on a scientific basis.

WITHDRAWAL TIME

In 2006, Barclay *et al*[54] were the first to report that colonoscopists with a mean withdrawal time of 6 minutes or more had higher detection rates of any neoplasia and advanced neoplasia. Since then, a recommended mean withdrawal time of at least 6 min has been formulated as a quality indicator in several colonoscopy guidelines[18-20].

However, colonoscopic withdrawal time as a quality indicator is not undisputed. Since the initial publication by Barclay *et al*[54], several observational studies have reported on the association between colonoscopic withdrawal time and the number of detected polyps[55-59]. Other large studies could however not confirm these findings[60-62]. Furthermore, interventions directed at optimizing withdrawal time, in an attempt to improve polyp detection, have yielded conflicting results. Although Barclay *et al*[63] did report higher rates of overall and advanced neoplasia detection during screening colonoscopy after implementing a time-dependent colonoscopic withdrawal protocol, other authors were not able to find a difference in overall polyp detection rate after formally implementing such a policy[64,65].

Gellad *et al*[66] were the first to study the association between withdrawal time during an initial, negative colonoscopy and the risk of developing neoplasia in the next five years. They did not detect any significant association. However, mean baseline withdrawal time in the 13 participating centers was rather long (greater than 12 min), possibly explaining the non-confirmatory results. It is possible that withdrawal time no longer is an adequate quality measure for screening colonoscopy above a certain threshold.

The use of the indicator withdrawal time is based on the assumption that endoscopists who take longer to withdraw the colonoscope also use specific techniques to improve visualization of the entire colonic mucosa. A study of two endoscopists with different rates of missed adenomas indeed showed that a better quality colonoscopic withdrawal technique was associated with a longer withdrawal time[67]. Lee *et al*[62] reported that the number of detected adenomas was found to be associated with the quality of withdrawal technique, but not necessarily related to withdrawal time. Withdrawal technique may therefore be a more important indicator for colonoscopy quality than withdrawal time. At present, there is however no generally accepted way to quantify an optimal withdrawal technique.

It is conceivable that the derived quality indicator withdrawal time in the future will be replaced by a measure of the proportion of the colonic mucosa that is adequately visualized during colonoscopy. Interestingly, Hong *et al*[68] recently reported on a fully automated three-dimensional reconstruction technique from individual colonoscopy images. Such a technique might eventually give real time feedback to the endoscopist on areas of the colonic wall that are not adequately inspected, thus enabling revisiting these areas during the same procedure. The percentage of the colon surface that is visualized by the endoscopist may potentially serve as a new quality indicator for colonoscopy. Furthermore, information on inspected and uninspected areas of the colonic wall may help in training endoscopists, giving insight in possible "blind spots" during scope withdrawal.

As mentioned above, the association between the quality indicator withdrawal time and the occurrence of interval cancers has not yet been elucidated.

ADENOMA DETECTION RATE

The adenoma detection rate (ADR) is defined as the proportion of screened subjects in whom at least one adenomatous lesion is identified[18,19,69]. In an asymptomatic screening population, an ADR of $\geqslant$ 25% in men and of $\geqslant$ 15% in women over 50 years old has been proposed in the American screening guidelines[18], whereas the British Quality Assurance Guidelines for Colonoscopy has set the standard ADR, based on their own pilot data, at $\geqslant$ 35% of all screening colonoscopies in patients who had a positive FOBT[19].

Repeatedly, considerable variations between endoscopists in the rate of detected polyps and adenomas have been shown[70-74]. The ADR is the only current quality indicator that has been demonstrated to be directly associated with interval colorectal cancer. In the landmark study by Kaminski *et al*[69], an ADR $\geqslant$ 20% was associated with a reduction in interval colorectal cancers. A recent study by Corley *et al*[75] showed that the ADR was inversely associated with the risk of interval CRC, but also with advanced-stage interval cancers and fatal interval cancers.

In line with these findings, many recent studies have focused on ways to optimize adenoma detection, ranging from inexpensive and easy to implement interventions in

Figure 1 Third-Eye retroscope.

daily clinical practice, to minor adaptations of currently used colonoscopy equipment to completely new colonoscopy platforms.

Position changes during colonoscope withdrawal have been reported to increase luminal distension and may reduce the rate of missed lesions[76]. Two small randomized studies have indeed suggested that dynamic patient position changes may improve polyp detection[77,78], but there was no difference in polyp or adenoma detection rates in another, larger randomized study[79].

Endoscopy nurse participation as a second observer during colonoscopy has been reported to significantly increase the overall number of detected polyps and adenomas found during colonoscopy[80], and appears an easy to implement intervention to increase polyp detection rate (PDR) and ADR[81].

Furthermore, the time of performing the colonoscopy may have an effect on the ADR. Testing the hypothesis that fatigue of the endoscopist, which increases as the day progresses, might affect ADR, Sanaka *et al*[82] were the first to report that the ADR of endoscopists was significantly higher in morning colonoscopies than in afternoon colonoscopies. The time of the colonoscopy during the day was an independent predictor for adenoma detection. These findings have been confirmed by almost all other studies on this subject[83-86]. Gurudu *et al*[83] proposed that colonoscopies should best be performed in half-day blocks by different physicians. They found no significant difference in ADR between morning and afternoon colonoscopies when endoscopists only perform colonoscopies in half-day blocks.

The use of high definition colonoscopy as compared to standard video colonoscopy has been reported to have only a marginal beneficial effect on the detection of colonic polyps and adenomas in a recent meta-analysis[87]. Due to heterogeneity of the included studies and the fact that no randomized trials were available, these results should be interpreted with some caution.

Virtual chromoendoscopy consists of multiple techniques that use a narrow spectrum of wavelengths with a decreased penetration depth to enhance visualization. Light of short wavelengths increases vascular contrast of the mucosa, potentially improving visualization and the identification of neoplastic lesions. Although there are some conflicting data, most studies and meta-analyses have not been able to demonstrate a substantial increase in ADRs with pan-colonic virtual chromoendoscopy[88-90].

Cap-assisted colonoscopy is performed by attaching a transparant cap to the tip of the colonoscope. These caps were originally designed to be used during endoscopic mucosa resection, but they might also aid in depressing colonic folds to improve visualization of the entire colonic mucosa. However, in a meta-analysis of 16 randomized controlled trials including 8991 subjects, Ng *et al*[91] concluded that cap-assisted colonoscopy only had a limited effect on ADR, although a higher proportion of patients with polyp(s) were detected when a cap was attached (relative risk 1.08; 95%CI: 1.00-1.17).

It has been reported that retroflexion of the colonoscope might aid in the removal of polyps that are difficult to access endoscopically[92,93]. Conceivably, inspection with a retroflexed colonoscope may also help in increasing visualization of the proximal aspects of colonic folds, especially in the right colon, and thereby increasing ADR. However, although this technique appears safe in experienced hands, both a randomized study and a large prospective observational study failed to demonstrate a relevant increase in the number of detected polyps[94,95].

In recent years, several new devices have been developed to improve visualization of the proximal sides of colonic folds and inner curvatures. First, the Third-Eye Retroscope® (Avantis Medical Systems, Inc) is a through-the-scope catheter with a camera and light source at the tip. After advancement through the working channel of the colonoscope, the catheter is retroflexed 180° (Figure 1). It then provides a 135° retrograde view of the colon. In a randomized, multicenter back-to-back study, the Third-Eye Retroscope yielded a net additional detection rate of 29.8% for polyps and 23.2% for adenomas compared to standard colonoscopy[96]. An advantage of this device is that it can be used with standard colonoscopy equipment. However, use of this device in clinical practice may be hampered by the fact that the Third-Eye Retroscope needs to be removed from the working channel in case a polypectomy snare or biopsy forceps is used. Furthermore, when the device is in place, the colonoscope has reduced suctioning capacity. These factors may increase procedural time and may be experienced as bothersome by the endoscopist.

Recently, Gralnek *et al*[97] reported the results of the first international, multicenter, randomized, back-to-back study with the new Full Spectrum Endoscopy™ platform (FUSE; EndoChoice®, Alpharetta, Georgia, United States). The full spectrum colonoscope allows a high resolution 330° view of the colonic lumen, as compared to the 140°-170° of standard colonoscopes (Figure 2). In their study including 185 subjects, the adenoma miss rate

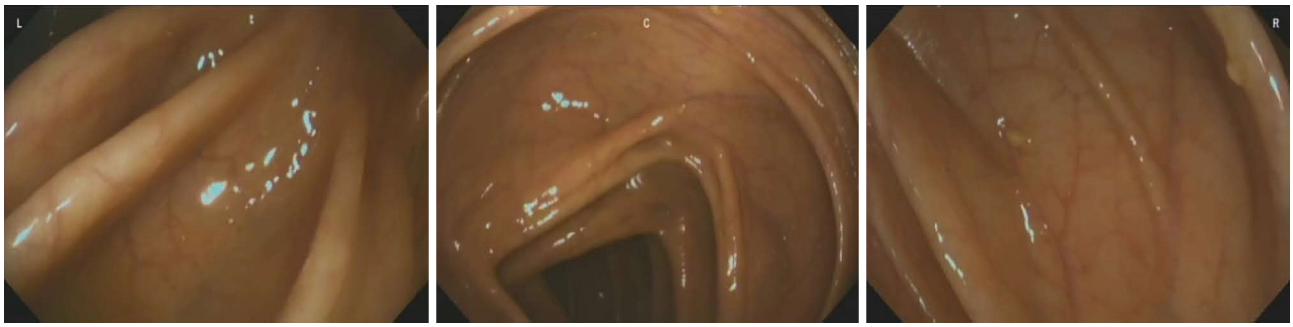

Figure 2 Endoscopic view using the Full Spectrum Endoscopy™ platform.

was significantly lower in patients in whom colonoscopy was performed with the full-spectrum endoscope first: in the latter group five (7%) of 67 adenomas were missed *vs* 20 (41%) of 49 adenomas in the group that underwent standard colonoscopy first ($P < 0.0001$). Although these results seem promising, further studies are required to determine the potential role for this system in non-expert centers. The obvious disadvantage in the implementation of this new device in daily clinical practice, is that new colonoscopes and main control units are required.

A potential downside of the current definition of ADR is that it does not discriminate between subjects in whom the endoscopist detects one *vs* more than one adenoma. It has been shown that physicians are more likely to miss additional adenomas during colonoscopy, when they have already detected two or more[4].

Wang *et al*[98] concluded that, despite comparable and adequate ADRs, there can be considerable variability between endoscopists with regard to the total number of adenomas detected per colonoscopy. They introduced a metric called the ADR-plus, the mean number of incremental adenomas after the first, and by coupling this to the ADR the authors were better able to distinguish high- from low-performing endoscopists. Lee *et al*[99] introduced two new measures in addition to the ADR that also may provide additional information on the inter-individual variation in the quality of performing colonoscopy: mean adenomas per procedure (MAP) and mean adenomas per positive procedure (MAP+). However, how these new metrics translate to the occurrence of interval cancers is currently not known.

PATIENT COMFORT AND SEDATION

Several guidelines recommend that sedation dosages as well as patient comfort scores should routinely be reported and monitored[19,20]. In their position statement on quality in screening colonoscopy, the European Society of Gastrointestinal Endoscopy proposed that no more than 1% of patients should have a saturation below 85% for more than 30 s or should require administration of a reversal agent[20].

Patient comfort in the screening setting is important, as patients who consider screening colonoscopy as being too uncomfortable, are less likely to participate[100]. It may obviously impact the effect of population screening when a significant proportion of the target population does not participate. Recently, Rostom *et al*[101] have prospectively validated a nurse-assisted patient comfort score in a multicenter, international setting, allowing for a uniform registration of patient comfort and comparison of colonoscopy practices. The various endoscopic societies have not yet adopted this validated comfort score. Which scores are considered acceptable and how to avoid drop-outs from the screening program has yet to be determined. Measuring comfort has the obvious caveat that endoscopists, nurses and patients may have different opinions about the level of (dis)comfort during the procedure.

Discomfort during colonoscopy can be reduced by the administration of sedatives. There is worldwide a large variation in the use of sedation for colonoscopy[102-105]. In some countries the majority of patients undergo colonoscopy unsedated, while elsewhere sedation with benzodiazepines combined with opiates is the standard of care. Entonox (nitrous oxide and oxygen) is frequently used in some countries, while elsewhere propofol and general anesthesia are increasingly being used in daily practice. Severe sedation-related complications have been reported to be rare: Behrens *et al*[106] reported a rate of 0.01% in their study of 388404 endoscopies. However, sedation-related adverse events need to be prevented, especially in an otherwise healthy screening population. There is however no validated score to record the level of sedation during colonoscopy, nor is there an accepted gold standard regarding sedation for colonoscopy.

Interestingly, a recent study from the United Kingdom screening program shows that, although there are wide variations in the use of sedation, colonoscopists' individual medication practice does not appear to be related to the occurrence of significant discomfort[102]. Instead, it is suggested that the best endoscopists cause less patient discomfort while using less sedation[103].

COMPLICATION RATE

Colonoscopy is an invasive procedure that inadvertently will lead to complications in a small subset of patients. The rate of complications obviously is not necessarily associated with the interval CRCs. However, for a

Table 1 Quality indicators and their shortcomings

Quality indicator	Proposed standard	Unresolved issues
Bowel preparation	Each endoscopy report should state the quality of the bowel preparation[18,19] ⩾ 90% of patients undergoing colonoscopy should have had a bowel preparation rated as excellent or at least adequate[19,20]	No evidence to support a cut-off of ⩾ 90% No clear and generally accepted definition of adequate bowel preparation Unclear what bowel preparation quality is the absolute minimum to detect relevant findings and prevent interval cancers No clear policy on how to proceed in case of inadequate bowel preparation
Cecal intubation rate	Overall cecal intubation rate of ⩾ 90%[18-20] Adjusted cecal intubation rate of ⩾ 95%[18,19] Cecal intubation rate of ⩾ 95% in all screening colonoscopies[18,19]	No robust scientific evidence to support a cut-off of ⩾ 90% No evidence supporting an association between cecal intubation rate and the occurrence of interval CRC
Withdrawal time	⩾ 6 min on withdrawal from cecal pole to anus[18-20]	Conflicting reports on the association between withdrawal time and the number of detected polyps Interventions directed at optimizing withdrawal time have yielded conflicting results No evidence supporting an association between withdrawal time and the occurrence of interval CRC Better endoscopic withdrawal technique is not necessarily associated with withdrawal time An indirect measure to quantify the proportion of the colonic mucosa that is adequately visualized
Adenoma detection rate	⩾ 25% in men and ⩾ 15% in women over 50 yr[18] ⩾ 35% of all screening colonoscopies in patients with a positive fecal occult blood testing[19]	The only quality indicator that has been shown to be directly associated with interval CRC Does not discriminate between subjects in whom the endoscopist detects one *vs* more than one adenoma Does not optimally differentiate between high- and low-performing endoscopists
Patient comfort and sedation	Routinely reporting and monitoring of patient comfort scores and sedation dosages[19,20]	Until recently no validated patient comfort score was available Not yet clear what patient comfort scores are considered acceptable The endoscopist, the nurse and the patient may have different opinions about the level of comfort during the procedure No gold standard regarding sedation during colonoscopy No validated score to assess the level of sedation during colonoscopy
Complication rate	Perforation in < 1:1000 colonoscopies[18-20] Post-polypectomy bleeding in < 1:100 colonoscopies with polypectomy[18,19]	Consensus based Complication rate is mainly dependent on the number of therapeutic colonoscopies, which may vary between screening strategies (colonoscopic screening of the entire population *vs* selection of high-risk individuals through fecal occult blood testing)

CRC: Colorectal cancer.

population screening program to have an overall beneficial effect, it is crucial that complication rates are low.

Perforation is the most serious complication of colonoscopy. It is defined as the presence of air, luminal contents or instrumentation outside the gastrointestinal tract[19]. It may result from mechanical trauma to the bowel wall, overinsufflation of the colon, or as a result of a therapeutic procedure. In the literature, reported overall rates of perforation range from 0.1%-0.6%[107-109]. The perforation rate for diagnostic colonoscopies is lower than that of therapeutic interventions. The British guidelines for screening colonoscopy state a standard of < 1:1000 risk of perforation in all colonoscopies[19,20], and a < 1:500 risk of perforation in colonoscopies in which polypectomy is performed[19]. This is largely consistent with the American guidelines[18], although it is important to keep in mind that there may be a significant variation in perforation risk between a screening population in which each participant undergoes a colonoscopy and a screening population that is pre-selected by means of fecal occult blood testing. Proportionally, it can be expected that more polypectomies will be performed in the latter. Each country should set its own standards according to the local screening strategy.

Historically, surgical closure or resection of the perforated colon segment was the only therapeutic option in case of iatrogenic colonic perforation. Several case series have reported on successful endoscopic closure of small iatrogenic bowel wall defects using metallic endoclips, either with endoclips alone or using a combined technique of endoclips and endoloops[110,111]. In recent years, the over-the-scope clip (Ovesco Endoscopy GmbH, Tuebingen, Germany) has become available, with high rates of successful perforation closure in the first reported case series[112,113].

Bleeding is the most common complication after polypectomy. Based on the literature, several guidelines set a standard of post-polypectomy bleeding in < 1:100 colonoscopies with polypectomy[18,19]. It is known that the risk of bleeding increases with size of the lesion and a more proximal location in the colon[114]. Several endoscopic techniques can be used to prevent bleeding. Cold snaring of small, non-pedunculated polyps may prevent delayed bleeding[115], even in anticoagulated patients[116]. Submucosal injection with saline and epinephrin prevents immediate bleeding but probably not delayed bleeding[117]. Furthermore, prophylactic placement

Table 2 Potential measures to improve performance per quality indicator

Quality indicator	Potential intervention to improve performance	Strength of scientific evidence
Bowel preparation	Split dose bowel preparation	Meta-analysis of randomized controlled trials
	Last ingested dose of PEG-solution 3-5 h before colonoscopy	Observational, prospective studies
Cecal intubation rate	Additional training and use of auxiliary endoscopic instruments (*e.g.*, pediatric colonoscope)	Expert opinion
Adenoma detection rate	Endoscopy nurse participation as a second observer	Randomized, multicenter studies
	Perform colonoscopy in the morning or in half-day blocks	Retrospective studies
	High definition colonoscopy (compared to standard video colonoscopy, marginal effect)	Meta-analysis
	Cap-assisted colonoscopy (marginal effect)	Meta-analysis of randomized controlled trials
	Third-Eye Retroscope	Randomized, multicenter study
	Full Spectrum Endoscopy	Randomized, multicenter study
Complication rate	Cold snaring of small, non-pedunculated polyps may prevent bleeding	Prospective, multicenter, observational study and small single center randomized controlled study
	Submucosal injection with saline and epinephrin prevents immediate bleeding	Randomized study
	Prophylactic placement of a detachable snare around the stalk of a pedunculated polyp prevents bleeding	Randomized studies
	Prophylactic closure of the polypectomy site with metallic clips after removal of large (> 2 cm) sessile or flat lesions may prevent bleeding	Retrospective study

of a detachable snare around the stalk of a pedunculated polyp may prevent bleeding[118,119], as well as prophylactic closure of the polypectomy site with metallic clips after removal of large (> 2 cm) sessile or flat lesions[120].

Post-polypectomy coagulation syndrome (PPCS), or transmural burn syndrome, is a known complication of colonoscopic polypectomy. It is defined by the development of abdominal pain, fever, leukocytosis and peritoneal inflammation in the absence of frank perforation that occurs after polypectomy with electrocoagulation[121]. To our knowledge, there is only one study that specifically focused on PPCS. In this large retrospective study, its incidence is reported to be 0.07% of all colonoscopies with polypectomy. Hypertension, a lesion size $\geqslant$ 10 mm and non-polypoid configuration of the lesion were independently associated with PPCS[121]. Correct identification of this entity is important, as this may avoid unnecessary explorative laparotomy. PPCS can usually be treated medically without a need for surgical intervention and without mortality. PPCS is not yet included in the current guidelines.

CONCLUSION

In summary, the main quality indicators for colonoscopy all have their shortcomings (Table 1). Most of these have been formulated based on consensus. Following the guideline Quality Indicators for Colonoscopy from the American Society of Gastrointestinal Endoscopy from 2006[18], many other countries have adopted these same quality indicators. The scientific evidence on which they are based is however limited. Potential measures to improve performance on individual quality indicators are summarized in Table 2.

What is not yet clear is how to proceed when a fellow or senior endoscopist does not meet the required standards. Individualized additional training or a binding negative advice to continue the fellowship could be an option for endoscopists in training. However, this could be difficult for senior endoscopists that have practiced for years, especially when the scientific basis for these quality indicators is still not well established. What further needs to be addressed, is how to check that endoscopists indeed perform colonoscopy according to the standard of care set by their peers or national guidelines.

ADR currently is the only quality indicator that has been shown to be directly associated with the outcome measure interval colorectal cancer. As such, it seems reasonable to let this indicator prevail in discussions with endoscopists who fail to meet the set standards.

Ideally, endoscopists should only be evaluated and compared by the most relevant outcome measure in the context of screening colonoscopies, i.e. the occurrence of interval CRCs. Since the incidence of interval CRCs is fortunately rather low, and the duration between colonoscopy and interval CRC is rather long, this may prove to be too slow and rigid a quality indicator in daily practice to timely intervene in case of substandard colonoscopy performance.

Until we find a better measure to approximate the risk of interval CRCs, the current set of quality indicators will have to suffice. However, they need to be interpreted with caution and continuously adjusted as more information becomes available. For instance, both withdrawal time and ADR are a derivative of the quality with which the entire colonic mucosa is visualized during colonoscopy and in time may be replaced with a more direct measure for the proportion of the colonic mucosa that is inspected.

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MINIREVIEWS

Myths, fallacies and practical pearls in GI lab

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Abstract

Many prevalent practices and guidelines related to Gastrointestinal endoscopy and procedural sedation are at odds with the widely available scientific-physiological and clinical outcome data. In many institutions, strict policy of pre-procedural extended fasting is still rigorously enforced, despite no evidence of increased incidence of aspiration after recent oral intake prior to sedation. Supplemental oxygen administration in the setting of GI procedural sedation has been increasingly adopted as reported in the medical journals, despite clear evidence that supplemental oxygen blunts the usefulness of pulse oximetry in timely detection of sedation induced hypoventilation, leading to increased number of adverse cardiopulmonary outcomes. Use of Propofol by Gastroenterologist-Nurse team is erroneously considered dangerous and often prohibited in various institutions, at the same time worldwide reports of remarkable safety and patient satisfaction continue to be published, dating back more than a decade. Of patient monitoring practices that have been advocated to be standard, many merely add cost, not value. Advances in the technology often are not incorporated in a timely manner in guidelines or clinical practices, *e.g.*, Capsule endoscopy or electrocautery during GI procedures do not interfere with proper functioning of the current pacemakers or defibrillators. Orthopedic surgeons have continued to recommend prophylactic antibiotics for joint replacement patients prior to GI procedures, without any evidence of need. These myths are explored for a succint review to prompt a change in clinical practices and institutional policies.

Key words: Endoscopy gastrointestinal; Pulse oximetry; Oxygen supplemental; Propofol; Conscious sedation; Deep Sedation; Fasting preprocedural; Standards of Care; Clinical Practice Guidelines

Core tip: Many prevalent endoscopic procedural practices and policies are not only unsupported by clinical and scientific evidence, but are counterproductive. Rather than enhancing patient safety and comfort, these increase risk and expense, introduce unnecessary delays. Evidence to reach proper decisions about these topics has been available for a while, but is not appropriately acknowledged and implemented. Avoiding these pitfalls can have a significant positive impact because these policies cover routine events, actions and decisions, including: required prolonged pre-procedural fasting, routine supplemental oxygen during sedation, prohibition of Propofol use by non-anesthesia personnel, multiple monitoring practices and prophylactic recommendations.

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MYTH

"The great enemy of the truth is very often not the lie-deliberate, contrived, and dishonest - but the myth - persistent, persuasive and unrealistic." - John F Kennedy.

A fallacy is a mistaken belief, based on flawed or incomplete data or an unsound argument. A fallacy,

once discredited, loses its force of persuasion, *e.g.,* the earth is flat. Without careful review of the key evidence contradicting a simplistic impression, someone new to a topic can easily come to an erroneous conclusion.

A Myth, on the other hand, is complex and tenacious. Despite conclusive refuting data and reasoning, myths can persist for an impressive period of time. In fact, some myths have resurgences and succeed in replacing established sound practices with erroneous ones.

History is replete with myths propounded by giants of their times.

Aristotle thought that while the heart was the seat of intelligence, the brain cooled the blood. He reasoned that humans are more rational than the beasts because, among other reasons, they have a larger brain to cool their hot-bloodedness!

Galen (second century), was one of the foremost physicians of his time. He deliberately engaged others in debate to prove them wrong. It is ironic that he made the practice of bloodletting a standard treatment that continued for more than a thousand years! That myth was responsible for more deaths from intervention than perhaps any other single medical procedure. On December 12, 1799, President George Washington developed a sore throat. As treatment, about three liters of his blood were removed from his body by venesection during a 10-16 h period (with his consent and at his request). He consequently died.

Modern medicine aspires to be evidence based, but there is a strong undercurrent of tradition and reverence for experts. Many of the clinical practices start as empirical attempts but then gain mythological flavor. Many guidelines are nothing more than intuitive opinions but are often rigidly enforced despite evidence indicative of lack of effectiveness or harm.

"Whatever is almost true is quite false, and among the most dangerous of errors, because being so near truth, it is more likely to lead astray." - Henry Ward Beecher.

In many GI labs around the world, the following myths and fallacies are currently believed and practiced, as reflected in the published articles, institutional policies and personal practice patterns. Their persistence serves as testament to the mythical and entrenched nature of these beliefs.

MYTH: PRIOR TO MODERATE SEDATION, OVERNIGHT FASTING IS EFFECTIVE AND ESSENTIAL FOR PREVENTION OF ASPIRATION

Prolonged pre-procedure fasting requirement, (regardless of the time of day when the procedure gets done) is a rigidly enforced "rule" in many institutions. Extensive review of literature has failed to show any statistical evidence of increased risk of aspiration despite recent oral intake, in relation to endoscopic and other moderate procedural sedation[1,2]. The myth of Nothing orally after midnight has persisted in many institutions.Some others have adopted an arbitrary 4-h fasting requirement. This frequently leads to delay and often inconveniences the patient. No research data has shown the value of even 2-h intake restriction[1,2].

The rationale provided is: (1) Oral intake leads to increased gastric content; (2) Gastric content is vomited during the sedation; and (3) Vomit is aspirated in the respiratory tract, creating a complication.

The clinically-observed facts are: Gastric content is not well correlated with recent intake[1], and may be low despite the intake or may be high despite fasting for extended duration, due to gastric retention. Endogenous gastric secretion and saliva add to it in variable amounts.

In the setting of GI bleeding, the stomach is often filled with blood and blood clots. People coming in with food bolus impactions and with a considerable amount of food in their stomachs have undergone emergency endoscopy without a high incidence of aspiration.

Vomiting and regurgitations are extremely rare during the endoscopic procedures under current procedural sedation and endoscopic techniques, even when significant gastric contents are present.

In the rare event of vomiting, aspiration is uncommon, partly because patients for endoscopic procedures are generally not in supine position, and many have some protective reflexes.

Stated differently: (1) Gastric contents: not well correlated with liquid intake after an hour or more; (2) Gastric contents: very low risk of vomiting; and (3) Vomiting: very low risk of aspiration.

Prohibition on chewing gum or similar extremely restrictive measures have no data or basis to support them.

A case can be made for usefulness of liberal clear liquid intake more than a couple of hours before the procedure: Proper hydration improves the patient's general well-being, helps avoid dehydration, and may make intravenous access easier.

The American Society of Emergency Physicians panel reviewed the scientific data and evidence related to pre-procedural sedation oral intake and made a policy change in 2005 to remove the requirement of fasting from moderate sedation, leaving the decision to the discretion of the treating physician[1].

Since then and until now, no increased incidence of aspiration-related complications has been observed or reported since then. After the more-recent follow-up review, the clinical policy was reaffirmed and kept unchanged[2].

Pearl

For diagnostic GI endoscopic procedures, it makes intuitive sense to instruct patients not to take solids immediately prior to Gastroscopy, as it will impair visualization. If for some reason this is not the case, then recent oral intake should not be considered an absolute contraindication. The oral intake status of

all patients should be reviewed and discussed with the patient, including the potential risk of aspiration even if the patient has been fasting. If, in the judgment of the treating physician, the benefits of the procedure far outweigh the potential risk of aspiration, and the patient consents and assumes the risk, then proceeding with the sedation and the procedure should be individualized and outcomes should be reviewed on an ongoing basis.

MYTH: PROCEDURAL SEDATION SHOULD INCLUDE ROUTINE ADMINISTRATION OF SUPPLEMENTAL OXYGEN TO INCREASE PATIENT SAFETY

Supplemental oxygen use is frequently (erroneously) advocated for procedural sedation in the GI lab. Often, its use is mandated by the institutional policy and is enforced for all patients.

However, those advocating this practice do not dispute the following: (1) When hemoglobin is near 100% saturated, additional fractional increase in the inspired oxygen cannot further increase oxygen content of the blood; (2) Pulse oximetry does not measure ventilation. It estimates oxygen saturation of hemoglobin. Alveolar ventilation serves the function of more than just oxygenation of the blood. CO_2 clearance from the lungs is the other major process; (3) There is a lag between onset of hypoventilation and development of hypoxemia as reflected by oxygen desaturation; and (4) The reason for the desaturation in this setting is not reduction in oxygen in the ambient environment, but due to the patient's hypoventilation induced by the sedative agents.

Oxygen supplementation is appropriate in the setting of low ambient oxygen: (1) Lack of oxygen in the ambient air; (2) Lower oxygen saturation; (3) oxygen supplementation; and (4) Improved oxygen saturation in the blood. High altitude physiological observations and studies have demonstrated that humans tolerate isolated very low oxygen saturation levels for short periods of time very well.

The myth of appropriateness of oxygen supplementation to treat hypoventilation-related desaturation is a fallacy because it does not take into account the etiology and pathophysiology of desaturation.

Pulse oximetry value is a proxy and an indirect indicator of alveolar ventilation, just as urine output is an indirect indicator of renal function. Instances of reduced urine output should not all be treated in the same way. Giving a diuretic to a dehydrated patient may temporarily increase the urine output, but it would be precisely the wrong thing to do.

Similarly, if supplemental oxygen is given, various ventilatory parameters worsen more than when compared to room air sedation. Niesters *et al*[3] demonstrated that while the deterioration in the ventilatory function was quite pronounced, the pulse oximetry continued to show normal readings.

In addition, it is insufficient to simply observe the patient's appearance and vitals to promptly and reliably detect the onset and extent of hypoventilation[4].

Fortunately, room air Pulse oximetry is quite sensitive in the detection of the onset of sedation-associated hypoventilation. It is a myth that capnometry offers any advantage over room air Pulse oximetry[5,6].

Supplemental oxygen prevents or delays oxygen desaturation resulting from hypoventilation induced by sedation. For similar reduction in pulse oximeter reading, hypercarbia is more pronounced in the setting of supplemental oxygen because of the longer duration of hypoventilation[7-9].

A supplemental oxygen-induced normal pulse oximetry reading creates a false sense of security for the person monitoring the patient and sets him or her up for a delay in the intervention directed towards improving ventilation in these early stages[10]. Desaturation is an effect: not to be "window dressed" without addressing the underlying process.

Due to hypoventilation, impaired clearance leads to increased partial pressure of CO_2 in the alveoli. Consequently, it becomes harder for the inspired oxygen to reach the alveoli, which may create a vicious cycle.

Inspired oxygen also reduces the hypoxic ventilatory drive, compounding the problem. Extreme elevation of CO_2 could produce CO_2 narcosis. Acute respiratory acidosis may develop with persistent hypoventilation.

It is a myth that short periods of hypoxemia, if detected and treated, improve clinical outcome. Review of available data of Pulse oximetry for perioperative monitoring has shown that researchers have repeatedly looked for such evidence and have not found it[11].

Hypoxemia is the effect of the hypoventilation, not the cause; therefore the measures solely directed towards delaying hypoxemia without addressing the hypoventilation will end up with higher likelihood of oversedation. In case of medications such as Midazolam and Fentanyl, the patient may continue to appear awake but progressive hypoventilation occurs. With propofol, early detection of hypoventilation is crucial in avoiding further dosing to stay within the therapeutic window.

The patients are appropriately advised to not use thick nail polish because it would reduce the sensitivity of the pulse oximetry sensor. It is remarkable that those who advocate avoidance of thick nail polish do not recognize the similarity between this recommendation and the fact that supplemental oxygen also markedly reduces the sensitivity and value of pulse oximetry in the setting of sedation.

The rationale given for using supplemental oxygen is that oxygen is essential for life; therefore, preventing any drop in oxygen saturation is a "safety" measure. However, a national study of cardiopulmonary unplanned events after GI endoscopy found that upon CORI (Clinical Outcomes Research Initiative) database review, routine use of supplemental oxygen was associated with significantly more Cardiopulmonary Unplanned

Events[12].

It is of concern that institutional policies and published studies have increasingly advocated and reported routine supplemental oxygen administration despite evidence that it is counterproductive has been available for more than a decade.

Pearl

Based on these facts and principles, the optimum approach may be to start sedation with the patient breathing room air (assuming no baseline hypoxemia on room air). The patient should be encouraged to take intermittent deep breaths to maintain ventilation. Airway management should be done as soon as the saturation drops by 4-6 points (from 100 to 96), as this is definitive evidence of hypoventilation and, therefore, the sedative effect. Avoidance or reduction of further sedative agent doses from this point onwards is prudent. If desaturation worsens, then ventilatory assistance along with supplemental oxygen is indicated. Oxygen alone, if ventilation is absent, does not correct the situation.

MYTH: SEDATION FOR GI PROCEDURES IN SLEEP APNEA PATIENTS IS VERY RISKY AND IS ASSOCIATED WITH A HIGHER INCIDENCE OF BAD OUTCOMES WITH STANDARD MONITORING

Indeed, patients with sleep apnea have added risk factors, but once known and incorporated in the management plan, current monitoring and care has produced equally good outcomes in this subset of the patients compared to non-sleep apnea patients[13-15].

Pearl

Patients with sleep apnea can safely receive procedural sedation, but they should be very closely watched as the risk of hypoventilation with sedation is higher and airway obstruction more likely. Room air pulse oximetry, small titrated doses, meticulous airway management and prompt use of reversal agents should be part of the plan.

MYTH: USE OF REVERSAL AGENTS DURING OR AFTER THE ENDOSCOPIC PROCEDURE IS A COMPLICATION, AND THE PATIENT MUST BE OBSERVED FOR LONGER PERIODS IN THE RECOVERY AREA DUE TO THE SIGNIFICANT RISK OF CLINICALLY DANGEROUS "REBOUND SEDATION"

Many institutions and regulatory agencies consider use of reversal agent such as Naloxone or Flumazenil to be "complications", requiring an incidence report that may even need to be reported to State regulatory agencies.

This myth implies that clinically inappropriate and avoidable oversedation must have occurred, because the reversal agent was required.

These policies and regulations also require extended intensive monitoring of these patients after use of a reversal agent, more than for other sedated patients who were not reversed. This policy is instituted to look for the mythical and dangerous "rebound sedation".

The following reasoning and data show that these are myths:

Sensitivity to the sedative agents is known to have a wide range of variability. A relatively small dose may lead to unexpected profound respiratory depression. In this setting, reversal of this effect is a safety measure, not a complication, *e.g.,* tapping on the brakes while driving through traffic is hardly proof of speeding.

There are times during many procedures, particularly colonoscopies, where increasing doses of Fentanyl or Midazolam are needed to counter the discomfort related to the pressure of the scope through a tortuous segment of the colon. However, once the discomfort has abated due to straightening of the colonic segment or at the end of the procedure, the unopposed residual sedative effects of these medications manifest due to the duration of the action of the drug. A reversal agent would promptly mitigate the effects of the drug. Moreover, ongoing analgesia after completion of the procedure is not needed, in contrast to after traditional surgery.

It is also a myth that these patients need to be routinely observed for extended periods (much longer than usual) after use of the reversal agent.

Bad outcomes due to Rebound sedation after reversal agent use, even after a massive overdose in the setting of poisoning, accidental or otherwise, are extremely rare[16,17].

Because titrated doses of short-acting sedatives are used in the GI lab, clinical practice experiences and reported studies in the medical literature have shown this practice to be very safe. Studies reporting routine use of reversal agents showed no clinically significant rebound sedation[18,19].

Resedation was reported in one study[20], but those patients remained clinically stable; return to the hospital and additional medical interventions were not required.

Pearl

The use of reversal agent is a safety measure. Despite the reversal agent having a shorter duration of action than the drug reversed, dangerous rebound sedation is not encountered in clinical setting due to continued metabolization and clearance of the sedative agent during this time.

Individualizing the observation based on clinically-unusual recovery is advisable over an indiscriminately prolonged observation policy after use of reversal agents.

MYTHS RELATED TO HOW MUCH MONITORING EQUIPMENT IS REQUIRED TO SAFELY PERFORM THE ENDOSCOPIC PROCEDURAL SEDATION

Current monitoring practices include Pulse oximetry, intermittent blood pressure recording, continuous electrocardiogram tracing, and, in some instances, Capnography and Bispectral Index.

In the United States Endoscopy labs, continuous cardiac monitoring is virtually universal. Around the world, this is not very common. The discrepancy has not been associated with any worsening of the outcome.

It is recommended that one nurse be dedicated exclusively to monitor the patient during sedation.

No studies have ever shown an outcome advantage from any of these recommendations of monitoring practices.

How much monitoring is sufficient to avoid sedation related serious complications? Külling *et al*[21] provided data in the setting of Propofol-based sedation in the GI lab without presence of anesthesia personnel.

This large study showed that by monitoring the patients with a Pulse oximeter alone, (no cardiac or blood pressure monitoring), along with a single nurse monitoring the patient as well as assisting the endoscopist, more than 27000 procedures were performed under gastroenterologist-directed Propofol, without significant complications.

Room air pulse oximetry has been demonstrated to be clinically as effective as Capnometry[6] and Bispectral Index[22] in monitoring for hypoventilation in these patients.

Pearl

Monitoring should be optimized. Room air Pulse oximetry along with good airway management may be sufficient for the vast majority of patients. Artifacts and malfunctions of monitoring devices (electrocardiogram, *etc.*) should not be allowed to become a distraction during the monitoring of endoscopic procedures.

MYTH: IMPLANTED DEFIBRILLATORS AND PACEMAKERS NEED TO BE RESET IF ELECTRO-CAUTERY IS USED DURING THE ENDOSCOPIC PROCEDURES

Implanted Defibrillators are commonly turned off and presumed to be at risk for accidental activation by electrocautery in many GI labs. This is an example of not incorporating the advances in technology and accumulated evidence into the current guidelines. Guidelines have remained in place for a long time after the technological changes have made them obsolete and erroneous. Devices currently in use are shielded and do not sense the electrocautery as a dysrhythmia[23,24].

Pearl

Newer Defibrillators and pacemakers do not require any adjustment for GI procedures. It is a good practice to avoid placing cautery pads close to the defibrillator device.

Despite initial concerns, Capsule endoscopy also has not been found to interfere with these devices, nor does pacemaker affects imaging done with Capsule endoscopy[25,26].

Capsule endoscopy may be safely undertaken in patients with pacemakers and implanted defibrillators.

MYTH: PROPOFOL USE UNDER THE DIRECTION OF GASTROENTEROLGISTS IS UNSAFE; ITS USE BY ANESTHESIA SPECIALISTS IS SAFER

This myth is quite prevalent in the United States and some other parts of the world, whereas in many other places, including Switzerland, increasing adoption of Propofol by the gastroenterologist has been reported[27]. On this issue, extensive data is available, spanning more than a decade. A team of a gastroenterologist and registered nurses has provided Propofol-based sedation with remarkable safety, excellent patient experience and without the additional cost of anesthesia personnel[28,29].

On the other hand, Gangi *et al*[30], in his study, found that Propofol given by anesthesia personnel was associated with a higher complication rate. This may be due to their practice of using larger doses (for induction of the General anesthesia that is followed by assisted ventilation), whereas the endoscopy patients are expected to breathe on their own[31].

The argument is commonly made that Propofol package insert restricts its administration solely to formally trained anesthesia personnel.

However, the actual phrase published by the manufacturer states:

"For general anesthesia or monitored anesthesia care (MAC) sedation, (emphasis added) DIPRIVAN Injectable Emulsion (Propofol) should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure." DIPRIVAN® (Propofol) INJECTABLE EMULSION, USP Fresenius Kabi USA, LLC Revised 5/14.

The gastroenterologists do not use Propofol for General anesthesia or MAC, and, therefore, the requirement of these abilities is not applicable in this setting[32-34].

For example, many primary physicians have acquired the skill to perform flexible sigmoidoscopy. Their use of a (longer) colonoscope in the GI lab would not be questioned or prohibited as long as the colonoscope is used to perform only flexible sigmoidoscopy.

Pearl

Propofol has been used by Gastroenterologists around the world for more than a decade with remarkable safety and patient satisfaction. It should be an option for interested and skilled physician and nurse teams. It should be undertaken after adequate training of the entire team. Patient safety should be the highest priority. This can be accomplished by learning the pharmacology of the drug and using small titrated doses (with or without combination with small doses of other agents that can be reversed) along with room air pulse oximetry to promptly detect hypoventilation.

MYTH: PROPOFOL LEADS TO DEEP SEDATION, WHEREAS NARCOTICS AND BENZODIAZEPINES PROVIDE MODERATE SEDATION

As reported by Patel *et al*[35], deep sedation frequently occurs in the GI lab with Narcotics and Benzodiazepines during sedation given by gastroenterologists and is routinely managed by them. On the other hand, Cohen *et al*[33] and Sipe *et al*[34] have reported that a moderate level of sedation is consistently achievable with low-dose Propofol-based sedation.

Many sedative agents, if given in large enough doses, lead to a state of general anesthesia. A general anesthetic, alcohol, has been available worldwide (over the counter) for centuries!

Pearl

Depth of sedation is age and dose dependent and exhibits a wide variability. The therapeutic effect and side effects are potentiated when these agents are combined. It is not the agent, but how and to what effect it is used that should be the focus.

MYTH: ENDOTRACHEAL INTUBATION SKILL IS NECESSARY FOR GI SEDATION WITH PROPOFOL

It is a myth because due to ultra short duration of action of the drug, and in the setting of smaller titrated doses, the transient respiratory depression from Propofol is likely to dissipate well before the intubation equipment can be assembled and used. If apnea does occur, then ambu bag ventilation is effective in assisting ventilation for a short duration.

Pearl

An ambu bag and oxygen should always be immediately available, and the team must practice regularly to stay skilled for its effective use. Early recognition of hypoventilation and proper airway management should further reduce the incidence of rare events when assisted ventilation is required.

MYTH: FOR PATIENTS WITH PROSTHETIC JOINTS, ENDOSCOPY FREQUENTLY LEADS TO INFECTION AND PROPHYLACTIC ANTIBIOTICS ARE ESSENTIAL

The Orthopedic Surgical Society has recommended giving antibiotics prior to endoscopic procedures[36].

However, current Endoscopy society guidelines[37], after reviewing the available clinical data, recommends against it.

Despite the fact that endoscopies without prophylactic antibiotics have been routinely performed worldwide for last several decades, without adhering to the Orthopedic Surgical Society recommendations, only a couple of joint infections have been reported in this setting, that could be coincidental.

The real and frequent risks and other implications of unnecessary antibiotic use must be weighed against this rare event. Antibiotics should not be given solely for an unproven theoretical protective effect[38].

Pearl

This issue should be discussed with each patient and the risk of infection should be put in proper perspective. This should help in avoiding prophylactic antibiotics of questionable benefit in this setting.

CONCLUSION

Neither "expert recommended" nor "increasingly adopted" practices and policies are immune from being fallacies and myths. In the Endoscopy suite, arguably the most significant inappropriate practice is the routine use of Supplemental oxygen because it is a practice contrary to the physiologic and scientific data with demonstrated adverse effects. It puts ventilatory monitoring by Pulse oximetry at a disadvantage. All of us should review in depth research on these issues and develop a mindset of continually questioning and re-examining the policies and practices in light of scientific data as well as technological advancements, *e.g.*, shielded implanted defibrillators related to electrocautery.

"The chief cause of poverty in science is imaginary wealth. The chief aim of science is not to open a door to infinite wisdom, but to set a limit to infinite error." Bertolt Brecht: Life of Gallileo.

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MINIREVIEWS

Endoscopic resection of subepithelial tumors

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Abstract

Management of subepithelial tumors (SETs) remains challenging. Endoscopic ultrasound (EUS) has improved differential diagnosis of these tumors but a definitive diagnosis on EUS findings alone can be achieved in the minority of cases. Complete endoscopic resection may provide a reasonable approach for tissue acquisition and may also be therapeutic in case of malignant lesions. Small SET restricted to the submucosa can be removed with established basic resection techniques. However, resection of SET arising from deeper layers of the gastrointestinal wall requires advanced endoscopic methods and harbours the risk of perforation. Innovative techniques such as submucosal tunneling and full thickness resection have expanded the frontiers of endoscopic therapy in the past years. This review will give an overview about endoscopic resection techniques of SET with a focus on novel methods.

Key words: Subepithelial tumors; Submucosal tumors; Gastrointestinal stromal tumors; Endoscopic resection; Endoscopic full thickness resection

Core tip: This review gives an overview about current endoscopic management of subepithelial tumors. Endoscopic resection techniques, available clinical data and potential indications will be discussed in detail. The review focuses on novel advanced techniques like submucosal tunnelling and endoscopic full thickness resection.

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INTRODUCTION

Subepithelial tumors (SETs) are mainly asymptomatic and incidentally found during endoscopic examinations in about 0.3% of cases[1]. The term "submucosal tumors" is widely used but incorrect as many tumors arise from or infiltrate deeper layers of the gastrointestinal (GI) wall. SET include a variety of benign, premalignant or malignant lesions. Although the majority of those lesions is benign, 13% are malignant[2].

Endoscopic ultrasound (EUS) has improved differential diagnosis of these tumors but a definitive diagnosis on EUS findings alone can be achieved in the minority of cases[3]. Hypoechoic tumors originating from the muscularis mucosae or the muscularis propria are consistent with leiomyomas or gastrointestinal stromal tumors (GIST). Although certain EUS criteria have been described to differentiate Leiomyomas and GIST[4], tissue sampling is generally needed to obtain definitive histologic diagnosis. For small tumors, diagnostic yield of EUS-guided biopsy is low[3]. Moreover, even if GIST is diagnosed, the amount of tissue gained is usually not sufficient to definitively determine mitotic count for appropriate risk stratification[5,6]. Therefore, complete endoscopic resection may provide a reasonable approach for tissue acquisition.

According to current NCCN guidelines, GIST $\geqslant$ 2 cm should be resected surgically whereas GIST < 2

cm lacking high-risk features in EUS can be followed-up periodically[7]. However, discrimination between "benign" and malignant GIST based on EUS-features may be difficult. Moreover, follow-up intervals are not well defined and many patients may not wish to undergo repeated life-long endoscopies. Therefore, European and Japanese guidelines recommend resection of histologically proven GIST even if size is < 2 cm[8,9]. Surgical resection is the gold standard for these tumors. However, endoscopic resection provides both a definitive histologic diagnosis (including risk stratification) and may also be an effective minimally invasive treatment for these potentially malignant lesions. Innovative advanced resection techniques such as submucosal tunneling and full thickness resection have expanded the frontiers of endoscopic therapy in the past years[10]. This review will describe endoscopic resection techniques of SET with a focus on novel methods.

ROLE OF EUS FOR CHOICE OF RESECTION MODALITY

As described above, EUS is a valuable tool for differential diagnosis of SET. In addition, thorough EUS-evaluation is mandatory to select the appropriate resection strategy depending on (1) tumor size: Tumor size can be determined exactly by EUS. With increasing size, endoscopic resection usually gets more demanding and may require advanced resection techniques. Moreover, peroral en bloc extraction of tumors > 3 cm may be difficult; (2) layer of origin: Exact determination of the originating layer or extent of tumor infiltration into the GI wall is mandatory for selection of resection modality. Basic resection techniques like cap-assisted resection suffice for tumors restricted to the submucosa. Resection of tumors originating from or infiltrating the MP is more challenging due to the risk of GI wall perforation. In these cases, EUS can also give information about the extent of tumor connection (broad or narrow) and depth of infiltration of the MP[11]; and (3) growth pattern: EUS can determine growth pattern with respect to the GI wall. Whereas tumors with intraluminal growth are usually suitable for endoscopic resection, tumors with predominantly extaluminal growth may require surgical therapy.

ENDOSCOPIC RESECTION TECHNIQUES

Snare resection

Small (1-2 cm) pedunculated or sessile SETs can be resected with a snare with or without prior injection[1]. One of the first series published reported on 45 patients with small submucosal lesions, all of which were resected successfully without any complications using a one or two channel endoscope (with a forceps to lift the lesion)[12]. A second series with 54 cases reported on diagnostic snare resection of submucosal tumors with a success rate of 100%, bleeding occurred in 9% of patients, no perforations were reported[13].

Cap-assisted submucosal resection

Cap-assisted submucosal resection is a simple and time-effective technique for small tumors limited to the submucosa. The tumor is sucked into a transparent cap and then resected with a mucosectomy snare preloaded in the cap. Alternatively, band ligation can be used to create a pseudopolyp prior to snare resection. Maximum size of the tumor is limited by the inner diameter of the cap which generally does not exceed 11 mm. In a study by Kajiyama *et al*[14] endoscopic submucosal resection without band ligation was reported to be feasible and effective for small esophageal leiomyomas originating from the muscularis mucosae. Feasibility of submucosal resection after band ligation was demonstrated by Wehrmann *et al*[15] in a prospective study for submucosal esophageal tumors. Maximum tumor size was 13 mm and R0-Resection was achieved in 10/11 cases. Lee *et al*[16] reported successful resection of esophageal lesions with a mean size of 7.1 mm (range 3-12 mm) with R0 resection in 96% and a mean procedure time of 5 min 26 s.

Endoscopic submucosal dissection

Endoscopic submucosal dissection (ESD) is an established technique for resection of gastric or colorectal neoplasms. After circumferential mucosal incision, step-by-step dissection of submucosal and muscular fibres with different electrosurgical knifes allows precise en-bloc resection of tumors. The technique has been used for resection of SET originating from the MP. In this context, it has also been called "endoscopic muscularis dissection", "endoscopic enucleation" or "endoscopic submucosal excavation"[10,17,18]. The largest study in this field was recently published by a He and colleagues. 145 patients with gastric SET arising from the MP with an average diameter of 15.14 mm (range 3-50) underwent ESD. Complete resection rate was 92%. Perforation occurred in 14%, all of which could be managed endoscopically[19]. A Chinese study included 143 patients with SET of the esophagogastric junction arising from the MP. Histologically complete en bloc resection could be achieved in 94.4%, perforation rate was 4.2%[20]. Other studies report success rates of 68%-100% with perforation rates of 2.4%-13.3%[21-26]. In conclusion, ESD appears to be an effective technique for resection of SET up to a size of 50 mm. However, the technique is technically demanding and may be time consuming. Moreover, for tumors arising from the MP, perforation rates up to 15% even in experienced hands have been reported. Lesions fixed to to the MP exhibit an increased risk of perforation when compared to lesions with a positive rolling sign[22]. Although extent of connection to the MP has not shown to be associated with increased risk of perforation[22], thorough EUS evaluation is mandatory prior treatment.

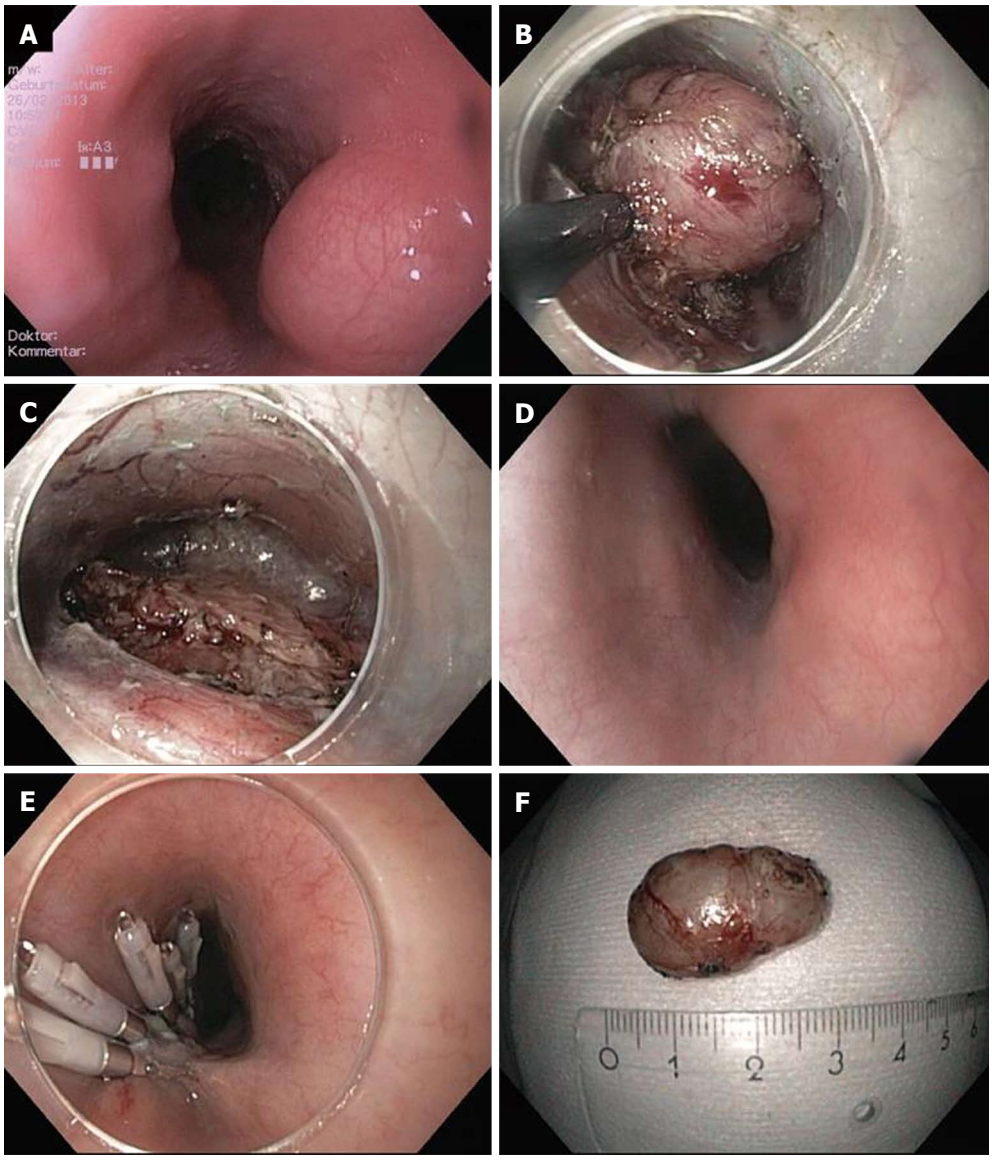

Figure 1 Submucosal endoscopic tumor resection/tunneling technique. A: Endoscopic image of lumen obstruction subepithelial tumor in the proximal esophagus in a 42 years old woman with dysphagia; B: After preparing the submucosal tunnel, the tumor gets visible and is enucleated in endoscopic submucosal dissection-technique with a TT knife. The tumor was arising from the muscularis propria; C: Resection site (endoscope in the submucosal tunnel). The muscularis propria is excised/perforated; D: Resection site (endoscope in the esophageal lumen. Intact mucosa completely covers the muscular perforation; E: The mucosal incision (about 5 cm proximal tot he resection site) was closed with standard clips; F: Resection specimen. Histological examination revealed a Leiomyoma, which had been R0-resected.

Submucosal endoscopic tumor resection/submucosal tunneling

The concept of "submucosal tunnelling" in the esophagus was initially described for peroral endoscopic myotomy (POEM) procedure by Inoue *et al*[27] in 2010. Only a few years later, this technique was applied for resection of subepithelial tumors in the esophagus and in the cardia[28,29]. In analogy to the POEM procedure, a mucosal incision at least 5 cm proximal to the tumor is created and the endoscope is introduced into the submucosal space. Then, the submucosal fibres are dissected until the tumor gets visible in the tunnel. The tumor is subsequently enucleated in ESD technique. During tunnelling and enucleation, it is crucial not to perforate the mucosa. After extracting the tumor from the tunnel, the mucosal incision is finally closed with standard clips (Figure 1).

Submucosal endoscopic tumor resection is especially suitable for tumors originating from or infiltrating into the MP. Compared to conventional ESD, a major advantage of this novel technique is that a mucosal layer covers the resection site and protects from mediastinitis/peritonitis when intended or accidental perforation of the MP occurs.

The largest study published to date included 85 SET (60 esophageal and 9 gastric). The tumors were mainly arising form the superficial MP (88.2%) and had a mean size of 19.2 mm (range 10-30 mm). Complete resection was achieved in 100% of cases with a mean procedure time of 57.2 min. Pneumothorax occurred

Figure 2 FTRD (Full Thickness Resection Device, Ovesco Endoscopy, Tübingen Germany). The device is assembled on a standard colonoscope. It consists of 14 mm modified over-the-scope clips which is mounted on a long transparent cap. A monofilament snare is preloaded in the tip of the cap. The handle of the snare runs on the outer surface of the endoscope underneath a transparent sheath. A grasping forceps or a tissue anchor can be advanced through the working channel of the endoscope.

in 7.1%, subcutaneous emphysema in 9.4% and pneumoperitoneum im 4.7%[30]. Other smaller studies reported success rates between 78% and 100% and complication rates between 13% and 33%[18,29,31,32]. The most common complications reported are pneumothorax, subcutaneous and mediastinal emphysema and pneumoperitoneum. While occurrence of pneumothorax generally requires a chest drain, air leakage into the mediastinum, the abdominal cavity and the subcutaneous tissue may not be considered as a "complication" rather than a natural consequence when the MP is perforated/resected. As long as the covering mucosa over the perforation is preserved, leakage of esophageal or gastric content is prevented. In the clinical studies published to date, no severe intraabdominal or mediastinal infections have been reported. Hence, submucosal endoscopic tumor resection using a tunnelling technique is feasible and relatively safe for tumors originating from the MP in the esophagus and cardia. Although a few gastric cases are also reported, submucosal tunnelling requires a relatively straight endoscope position and may not be applicable for tumors in locations like the fundus or proximal corpus.

Endoscopic full thickness resection

For SET arising from or infiltrating deep layers of the MP, full thickness resection may be necessary to achieve complete removal of the tumor. As full thickness resection naturally results in a GI wall perforation, secure and effective defect closure is mandatory. Generally, there are two different approaches for endoscopic full thickness resection (EFTR): (1) Full thickness resection followed by endoscopic defect closure; and (2) Creation of GI wall duplication (with serosa-to-serosa apposition) followed by EFTR.

Zhou *et al*[33] reported full thickness resection of 26 gastric SETs arising from the MP. Resection/enucleation of the tumors was performed using ESD technique and the gastric wall defect was closed with standard clips. Mean tumor size was 2.8 cm (1.2-4.5 cm). Complete resection rate was 100% with a mean procedure time of 105 min; no major complications were reported. Another study from 2013 reported 20 on a similar resection technique in 20 patients. In this study, the wall defects were closed with clips and endoloops[34]. *En bloc* resection rate was 100% without severe complications. A Chinese study reported on 42 gastric stromal tumors which were resected either by EFTR with secondary clip closure or laparascopically. In this non-randomized study, complete resection rate, operation time, length of hospital stay and complications were not statistically different in both groups[35].

Although the studies mentioned report excellent results with no serious complications, it must be emphasized that defect closure with standard clips may only be possible for small perforations. Moreover, concerns have been raised whether closure of only the mucosal layer is sufficient after EFTR[36]. Von Renteln and colleagues compared closure of natural orifice transluminal endoscopic surgery (NOTES) gastrostomies by either conventional or over-the-scope clips (OTSC) in a porcine study with 20 pigs[37]. In the conventional clip group, 3 minor and 1 major leaks were observed and four pigs developed peritonitis. In the OTSC group, no leaks were observed and microscopic evaluation showed that OTSC led to a deeper defect closure within the submucosal or muscular layer. Multiple clinical studies have shown effectivity of OTSC for durable closure of GI wall perforations[38]. EFTR with consecutive defect closure with OTSC was clinically evaluated in the EndoResect study[39]. Twenty patients with gastric SET $\leqslant$ 3 cm were enrolled; six tumors could not be resected endoscopically due to large size or extraluminal growth. The other tumors were resected using a double channel endoscope, a tissue retractor and a monofilament snare. Perforation occurred in six cases, all of which could be closed by OTSC application; mean procedure time was 44 min. Although this approach is very interesting because of its technical simplicity, most of the procedures in the study were done under laparoscopic control. Moreover, OTSC application requires secure apposition of the borders of the gastric defect which may not be possible in case of large perforations.

Even if clinical data suggest that EFTR with secondary defect closure is feasible and safe, secure closure of the GI wall may be technically demanding and strongly depends on the skills and the experience of the endoscopist[10]. Therefore, securing GI wall patency before resection (in analogy to laparoscopic wedge resection) may be an interesting and potentially safer approach. The concept of OTSC application over a SET followed by snare resection above the clip was recently reported by a United States group[40,41]. Lesions were located in the duodenum, in the esophagus, in the stomach and in the rectum. After application of an 11 mm OTSC, all lesions could be resected successfully. R0-resection was achieved in 7/8 cases. A drawback of this

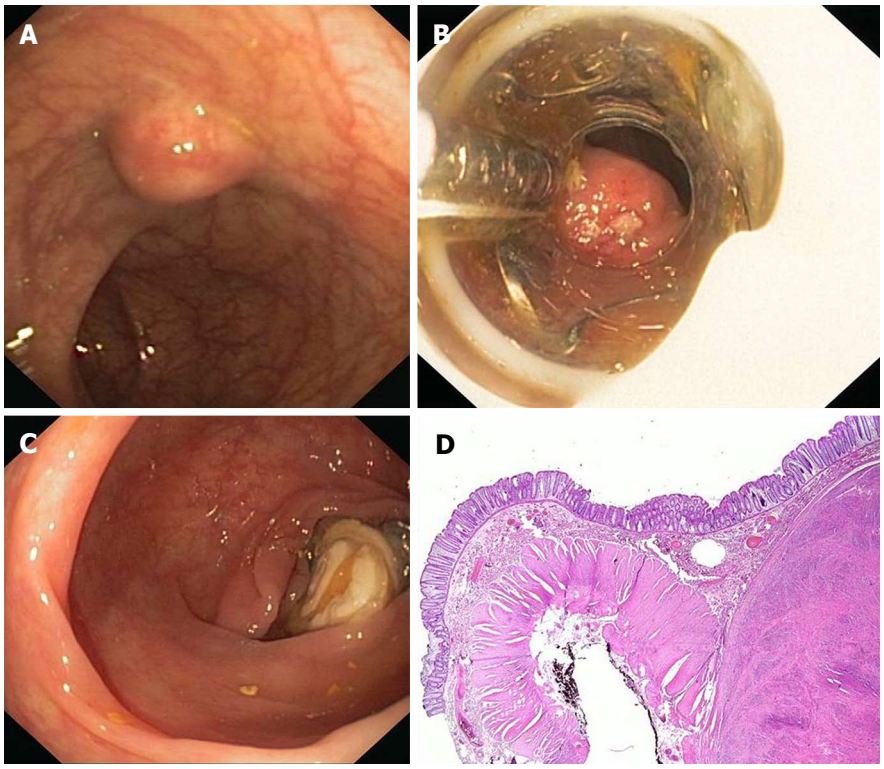

Figure 3 Endoscopic full thickness resection with the FTRD. A: A 75 years old woman presented with a 1.5 cm subepithelial tumor in the descending colon; B: Endoscopic view with the FTRD mounted on a standard colonoscope; C: Resection site after endoscopic full thickness resection. The over-the-scope clips secures colonic wall patency; D: Histologic image (HE-staining) of the resection specimen showing one lateral resection margin. Note the cross-sectional view of the whole colonic wall on the left side. The tumor (leiomyoma) is shown on the right.

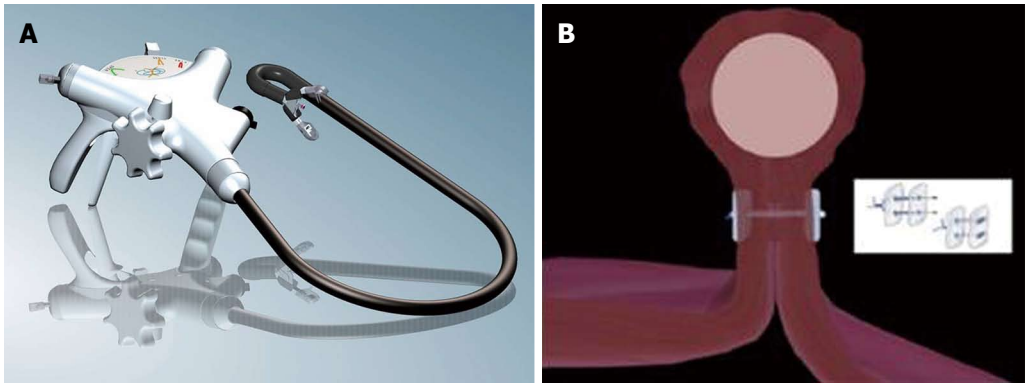

Figure 4 Endoscopic full thickness suturing. A: The GERDX suturing device (G-Surg, Seeon, Germany); B: Schematic illustration of full thickness suturing. Application of PTFE-pledgeted sutures underneath the tumor creates a gastric wall duplication with serosa-to-serosa apposition.

technique is that the size of the cap limits the maximum size of the lesion (mean size in the study was 13.4 mm). A novel over-the-scope device (FTRD, Ovesco Endoscopy) uses a modified 14 mm OTSC mounted on a long transparent cap with a preloaded snare (Figures 2 and 3)[42-45]. This device has been designed for one-step full thickness resection using a clip-and-cut technique. Due to the larger diameter of the OTSC and the longer cap, resection of larger lesions is possible compared to the standard OTSC system. The device was investigated by von Renteln *et al*[44] for resection of artificial submucosal lesions in a porcine study. The OTSC was able to close the resection site completely in all cases, however, EFTR was achieved in 50% of cases only. This is probably due to the fact that the thick gastric wall can often not fully be incorporated into the cap with its inner diameter of 13 mm. Another drawback of the device is its large outer diameter of 21 mm which hampers peroral introducability. Two porcine studies evaluated the device for use in the colon and showed that EFTR was feasible with efficient OTSC closure of the defects. Maximum size of resection specimen was 30 and 40 mm. In our first clinical experience (25 patients, manuscript submitted), colorectal EFTR with the FTRD was effective and safe. Due to the limitations in the upper GI tract, the FTRD is currently CE marked exclusively for colorectal EFTR.

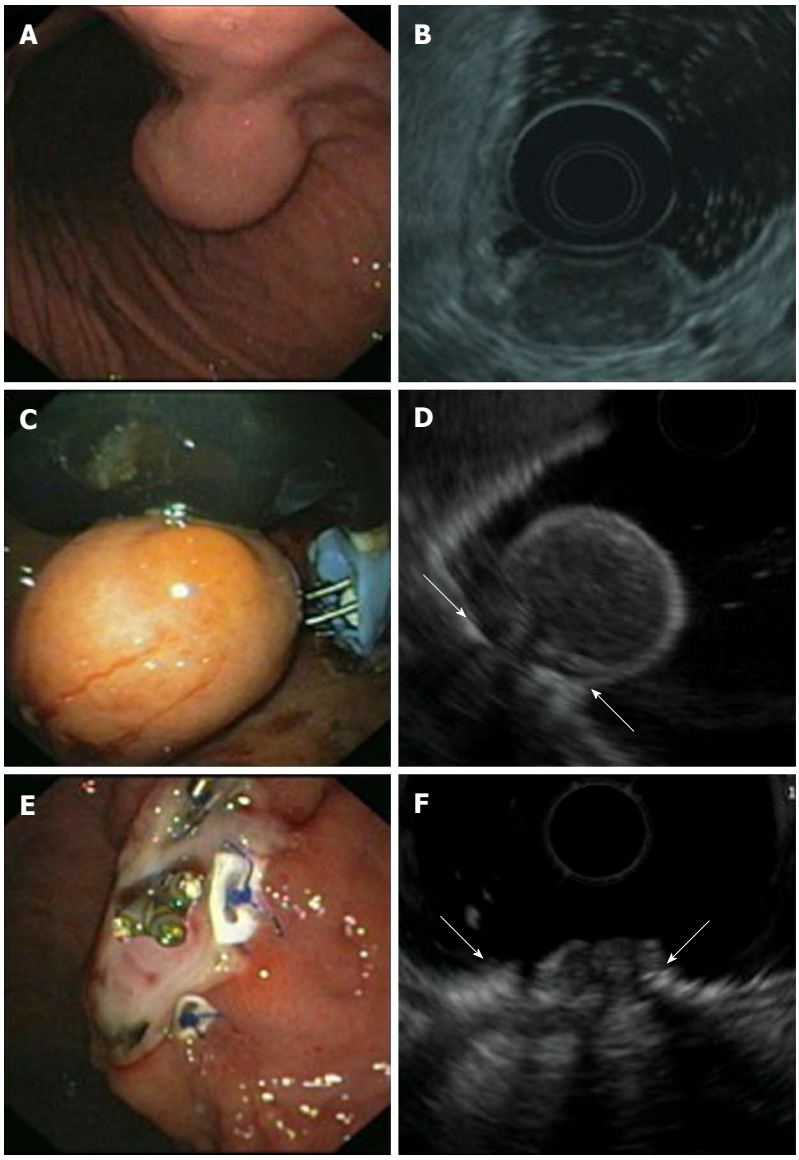

Figure 5 Endoscopic full thickness resection of gastric gastrointestinal stromal tumors after transmural suturing. A: Subepithelial tumor in the gastric corpus; B: Endoscopic ultrasound (EUS) showed a hypoechoic tumor originating from the muscularis propria with a maximum diameter of 27 mm; C: Two transmural sutures underneath the tumor were applied using the Plicator™ suturing device; D: EUS image of the pseudopolyp after suturing. Arrows are indicating the sutures; E: The tumor was resected with a snare above the sutures. The transmural PTFE-pledgeted sutures are securing gastric wall patency. Resection was macroscopically complete; F: EUS image of the resection site. Arrows are indicating the sutures. There was no evidence of residual tumor.

In 2008, our group reported on the concept of applying transmural sutures underneath the tumor prior EFTR for the first time. Two transmural PTFE-pledgeted sutures were placed underneath the tumor using a device originally designed for endoscopic anti-reflux Therapy (Plicator™, NDO Surgical, Inc, Mansfield, Mass) thereby creating a full thickness duplication with serosa-to-serosa apposition (Figure 4). The tumor was then resected with a monofilament snare above the suture (Figure 5)[46]. In 2011, a second series with three patients undergoing successful EFTR with the use of resorbable sutures was published[47]. In the meantime, our group has applied this technique for EFTR of subepithelial gastric tumors in a total of 31 patients [Schmidt *et al*, manuscript accepted in Endoscopy]. Mean tumor size was 20.5 mm (range 8-48). Macroscopically complete en bloc resection could be achieved in 100%, R0-resection rate was 90.3% with a median procedure time of 60 min. Perforation occurred in three patients; in all cases, the defect was successfully closed by application of additional transmural sutures. When compared to OTSC application before resection, this method is applicable for tumors up to a size of about 4 cm. Moreover, it is feasible in almost every location in the stomach. As the suturing device was originally designed to work in retroflex position, the technique is especially suitable for tumors in the proximal corpus, cardia and even in the fundus. In comparison to the clip closure techniques described above, patency of the gastric wall is secured not only by mucosal closure but rather by full-thickness suturing with serosa-to-serosa apposition. This technique meets surgical standards for defect closure and may result in a more durable gastric

wall repair especially for resection of large tumors. The suturing device can not only be used for suturing prior resection but also for secondary perforation closure[48]. A major limitation of EFTR after transmural suturing is the need of special endoscopic equipment. The Plicator™ device from NDO is not any more commercially available. However, a new CE-marked single-use device is available in Europe now (GERDX™, G-Surg, Seeon, Germany). This device was used for the last two cases in our series and seems to be as effective as the Plicator™.

CONCLUSION

Surgical resection is still standard of care for resection of malignant SET. However, novel advanced resection and closure techniques have led to shift from mucosal and submucosal resections towards intramural and transmural endoscopic interventions. Although clinical data is still very limited, the results published so far are promising. However, prospective comparative studies are necessary to further evaluate efficacy, safety, and long-term outcome of these techniques.

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RETROSPECTIVE STUDY

Narrow-band imaging observation of colorectal lesions using NICE classification to avoid discarding significant lesions

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Abstract

AIM: To assess the risk of failing to detect diminutive and small colorectal cancers with the "resect and discard" policy.

METHODS: Patients who received colonoscopy and polypectomy were recruited in the retrospective study. Probable histology of the polyps was predicted by six colonoscopists by the use of NICE classification. The incidence of diminutive and small colorectal cancers and their endoscopic features were assessed.

RESULTS: In total, we found 681 cases of diminutive (1-5 mm) lesions in 402 patients and 197 cases of small (6-9 mm) lesions in 151 patients. Based on pathology of the diminutive and small polyps, 105 and 18 were non-neoplastic polyps, 557 and 154 were low-grade adenomas, 18 and 24 were high-grade adenomas or intramucosal/submucosal (SM) scanty invasive carcinomas, 1 and 1 were SM-d carcinoma, respectively. The endoscopic features of invasive cancer were classified as NICE type 3 endoscopically.

CONCLUSION: The risk of failing to detect diminutive and small colorectal invasive cancer with the "resect and discard" strategy might be avoided through the use of narrow-band imaging observation with the NICE classification scheme and magnifying endoscopy.

Key words: Image-enhanced endoscopy; Narrow-band imaging; Resect and discard; NICE classification; Magnifying endoscope; Colonoscopy; SM-d

Core tip: Discarding a polyp without performing histological evaluation runs the risk of failing to detect small invasive colorectal cancer. Retrospectively, we aimed to assess the risk of failing to detect diminutive and small colorectal invasive cancer with the "resect and discard" strategy by using the NICE classification scheme with a magnifying endoscope. We reviewed and assessed 878 polyps less than 1 cm in diameter detected in our hospital. Among them, 2 SM-d carcinomas were found and both of their optical features were classified as NICE type 3. We concluded

that the risk of failing to detect diminutive and small invasive colorectal cancer with the "resect and discard" strategy might be prevented by employing NICE classification under narrow-band imaging magnification.

Hattori S, Iwatate M, Sano W, Hasuike N, Kosaka H, Ikumoto T, Kotaka M, Ichiyanagi A, Ebisutani C, Hisano Y, Fujimori T, Sano Y. Narrow-band imaging observation of colorectal lesions using NICE classification to avoid discarding significant lesions. *World J Gastrointest Endosc* 2014; 6(12): 600-605 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i12/600.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i12.600

INTRODUCTION

Removal of all adenomatous polyps during colonoscopy has been standardized worldwide. As the National Polyp Study (NPS) demonstrated that removal of all adenomatous polyps could significantly reduce colorectal cancer incidence and mortality[1], it has been standard practice for all polyps to be retrieved and submitted for pathological evaluation. Recently, however, the "resect and discard" policy was advocated[2,3]. According to this strategy, a hyperplastic polyp in recto-sigmoid colon would be left to reduce the risk of polypectomy, and diminutive (1-5 mm) or small (6-9 mm) lesions would be resected and discarded to eliminate the costs associated with histological evaluation. However, discarding polyps without performing histology runs the risk of failing to detect diminutive and small colorectal invasive cancer, which would otherwise be received surgery. Recently, the NICE classification was proposed as a valid tool for not only differentiating hyperplastic from adenomatous polyps, but also predicting SM-d carcinomas in colorectal tumors[4,5].

The aim of this study was to investigate the risk of failing to detect diminutive and small colorectal invasive cancers in real-time using the "resect and discard" strategy with NICE classification and magnifying endoscopy.

MATERIALS AND METHODS

Patients

Consecutive patients who underwent colonoscopy and received polypectomy in our institution were recruited in the retrospective study.

Colonoscopy procedure

For bowel preparation, patients ingested 1.5 to 2 L of polyethylene glycol solution in the morning before the procedure. Six colonoscopists performed all colonoscopy procedures up to the cecum with high-resolution endoscope (CF-H260AZI; Olympus, Optical Co., Ltd., Tokyo, Japan) and NBI magnification. We used a video endoscope system (EVIS LUCERA SPECTRUM; Olympus, Optical Co., Ltd., Tokyo, Japan) and a digital image filing system (SolemioENDO; OLYMPUS, Tokyo, Japan). In NBI mode with this system, the center wavelengths of the dedicated trichromatic optical filters are 540 and 415 nm, with bandwidths of 30 nm. We set the optical enhancement at enhancement mode A8 and color mode 3. Macroscopic type of the lesions were based on the Paris classification of superficial gastrointestinal lesions[6].

Endoscopic diagnosis using the NICE classification

All of the lesions were initially detected by conventional view, and then examined by NBI with magnification to evaluate the endoscopic features on the surface. All lesions were then classified into 3 types based on NICE classification, which consists of 3 types as shown in Table 1 and Figure 1[4,7].

Clinicopathological evaluation

We reviewed medical records using SolemioENDO colonoscopy system and detected polyps less than 1 cm in diameter, and we aggregated the lesion size data (1-5/6-9 mm), location (right/left-side), shape (pedunculated/sessile/flat/depressed), NICE classification category, and pathological diagnosis. The incidence of diminutive and small invasive colorectal carcinoma and their endoscopic features were also assessed.

RESULTS

Patient characteristics and clinicopathological features of resected lesions

A total of 878 polyps less than 1 cm in diameter were detected in 468 patients. Among the cohort, 290 patients were male, 178 were female, and average age was 66.3 years old (32-97, SD). The average value of polyp size was 4.7 mm (1-9, SD) and 542 of them were detected in the right-side colon, while 336 were detected in the left side. A total of 12 polyps were pedunculated, 274 were sessile, 590 were flat, and 2 were depressed in shape. Based on histology, 123 were non-neoplastic polyps [100 hyperplastic, 13 Sessile Serrated Adenoma/Polyp (SSA/P), 10 other], 753 were adenomas (717 tubular, 26 tubulovillous, 10 serrated), and 2 were invasive cancers.

Relationship between endoscopic diagnosis using the NICE classification and pathological diagnosis

Among the 2 groups divided based on polyp size (diminutive and small), we detected 681 diminutive polyps in 402 patients and 197 small polyps in 151 patients. The 681 diminutive polyps consisted of 105 non-neoplastic polyps, 557 low-grade adenomas, 18 high-grade adenomas or intramucosal/SM scanty invasive carcinomas, and 1 SM-d carcinoma. Additionally, the 197 small polyps consisted of 18 non-neoplastic polyps, 154 low-grade adenomas, 24 high-grade adenomas or intramucosal/SM scanty invasive carcinomas, and 1 SM-d carcinoma. The optical features of invasive cancer could

Table 1 Narrow-band imaging International Colorectal Endoscopic Classification[1]

	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels may be present coursing across the lesion	Brown vessels surrounding white structures[2]	Has area(s) of disrupted or missing vessels
Surface Pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular or branched white structures surrounded by brown vessels[2]	Amorphous or absent surface pattern
Most likely pathology	Hyperplastic	Adenoma[3]	Deep submucosal invasive cancer
Treatment	Follow up	Polypectomy/EMR/ESD	Surgical operation

[1]Can be applied using colonoscopes with or without optical (zoom) magnification; [2]These structures (regular or irregular) may represent the pits and the epithelium of the crypt opening; [3]Type 2 consists of Vienna classification types 3, 4 and superficial 5 (all adenomas with either low or high grade dysplasia, or with superficial submucosal carcinoma). The presence of high grade dysplasia or superficial submucosal carcinoma may be suggested by an irregular vessel or surface pattern, and is often associated with atypical morphology (*e.g.*, depressed area).

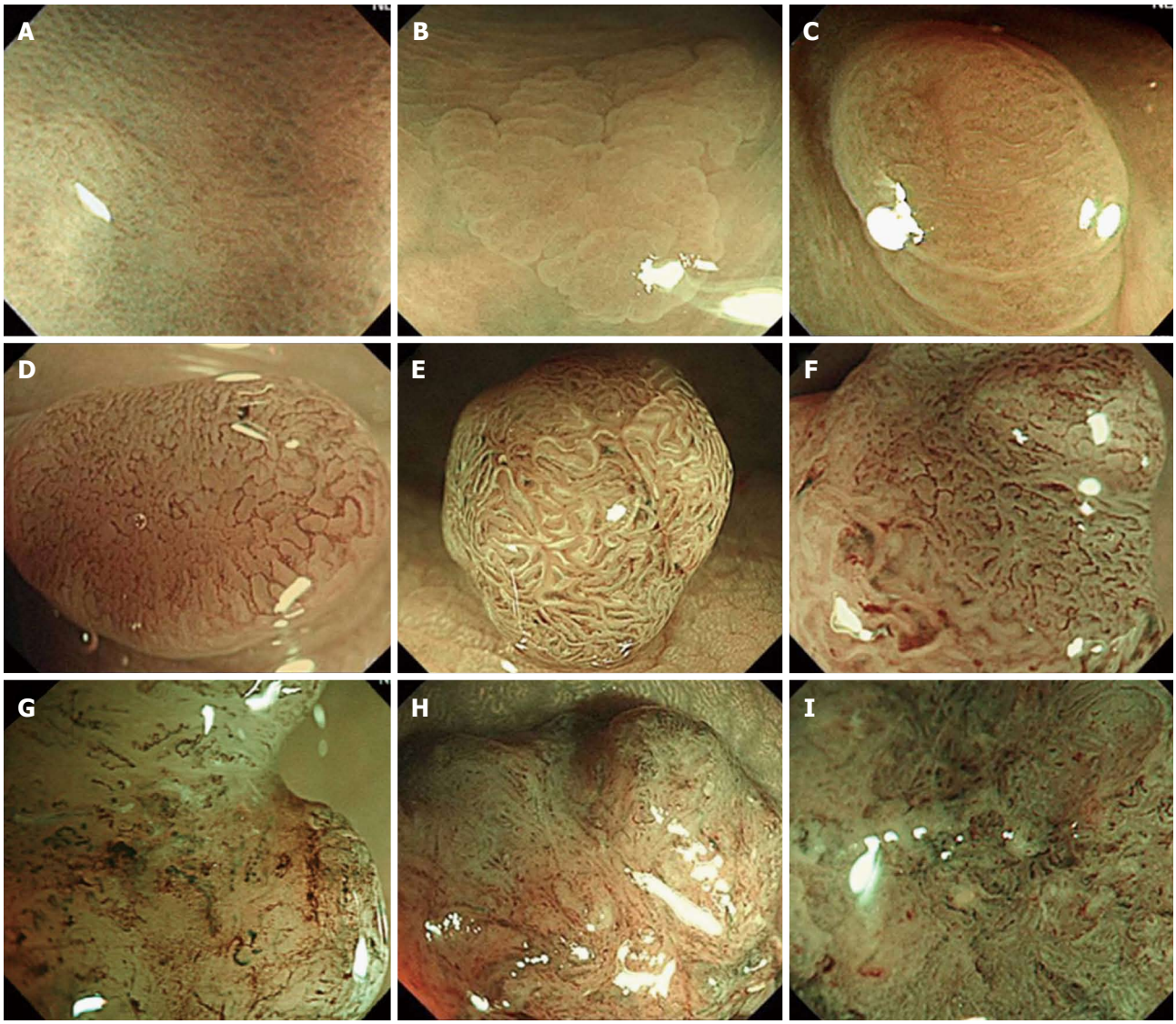

Figure 1 Endoscopic findings of narrow-band imaging observation with magnifying endoscopy. A-C: Lesions classified as NICE type 1; D-F: Lesions classified as NICE type 2; G-I: Lesions classified as NICE type 3.

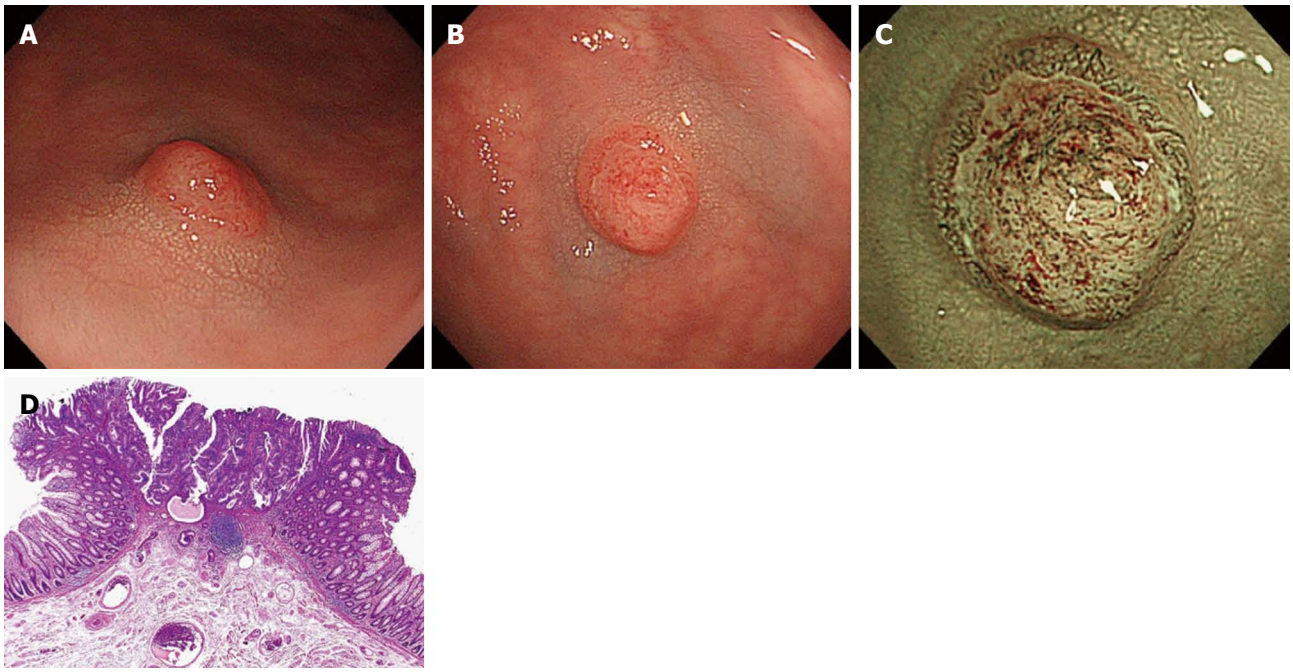

Figure 2 Invasive cancer 1 (S/C, 4 mm, Ⅱa + Ⅱc, Depressed type with NICE type 3). A and B: 0-IIa+IIc lesion was shown in sigmoid colon; C: NBI-magnifying endoscopy showed the feature classified as NICE type 3; D: Pathological diagnosis was well differentiated tubular adenocarcinoma, pSM-M, ly(+), v(-), budding grade 0-1.

be diagnosed as NICE type 3 endoscopically (Figures 2 and 3).

DISCUSSION

Morson[8] described the adenoma-carcinoma sequence in detail, which led to recognition among clinicians worldwide of the course of progression from adenomas to colorectal cancers. Removal of all adenomatous polyps during colonoscopy has been standardized worldwide. As the NPS demonstrated that removal of all adenomatous polyps could significantly reduce colorectal cancer incidence and mortality[1]. At present, it is routine practice to retrieve polyps for pathological evaluation because the accuracy of diagnosis to distinguish non-neoplastic from neoplastic colorectal lesions under observation with white light is not high and usually has a limit of 59% to 84%[9-14].

Image-enhanced endoscopy including NBI was introduced in 2006 and its use has since spread widely and rapidly worldwide, which contributed to improved diagnostic precision even without the use of magnification[15]. Furthermore, the introduction of a concept called the "confidence level" has further improved diagnostic precision.

According to this concept, cases are classified as high confidence (HC) or low confidence (LC), based on the degree of diagnostic certainty. It has already been proven that diagnostic precision is enhanced when only HC cases are subjected to endoscopic diagnosis[2,3]. It was reported that the accuracy rate of diagnosis to distinguish non-neoplastic from neoplastic colorectal lesions improved over 90% in 2009 at academic centers in the United Kingdom and United States through the use of NBI (non-magnifying) for HC cases. In other words, the accuracy of endoscopic diagnosis with HC can be comparable to that of pathological diagnosis. Recently, the "resect and discard" policy was advocated[2,3]. According to this strategy, a hyperplastic polyp in recto-sigmoid colon would be left to reduce the risk of polypectomy, and diminutive or small adenomas would be resected and discarded so as to eliminate the cost of pathological examination. However, discarding polyps without performing histology increases the risk of failing to detect diminutive and small colorectal invasive cancers, which would otherwise be received surgery, and if a recto-sigmoid polyp is left *in situ*, there is a risk of leaving behind a neoplastic lesion if the diagnosis is incorrect.

In the present study, among 878 polyps less than 1 cm in diameter, 2 SM-d carcinomas were identified (Tables 2 and 3). One had a diameter of 4 mm and the other, 6 mm. Both were in the sigmoid colon, with the shape of Ⅱa + Ⅱc, depressed type, and had optical features of invasive carcinoma classified as NICE type 3. Consequently, these 2 patients received adequate surgical treatment (Figures 2 and 3). Additionally, we diagnosed 53 diminutive and 21 small polyps classified as NICE type 1, meaning that they were non-neoplastic and would, according to the "resect and discard" strategy, be left *in situ* if located in the recto-sigmoid colon (Table 3). Of these polyps, 11 diminutive polyps and 9 small polyps were adenomas. The rate of false diagnosis was not low, presumably because the study was not prospective and cases included not only HC cases but also LC cases. Nonetheless, all of the adenomas diagnosed as

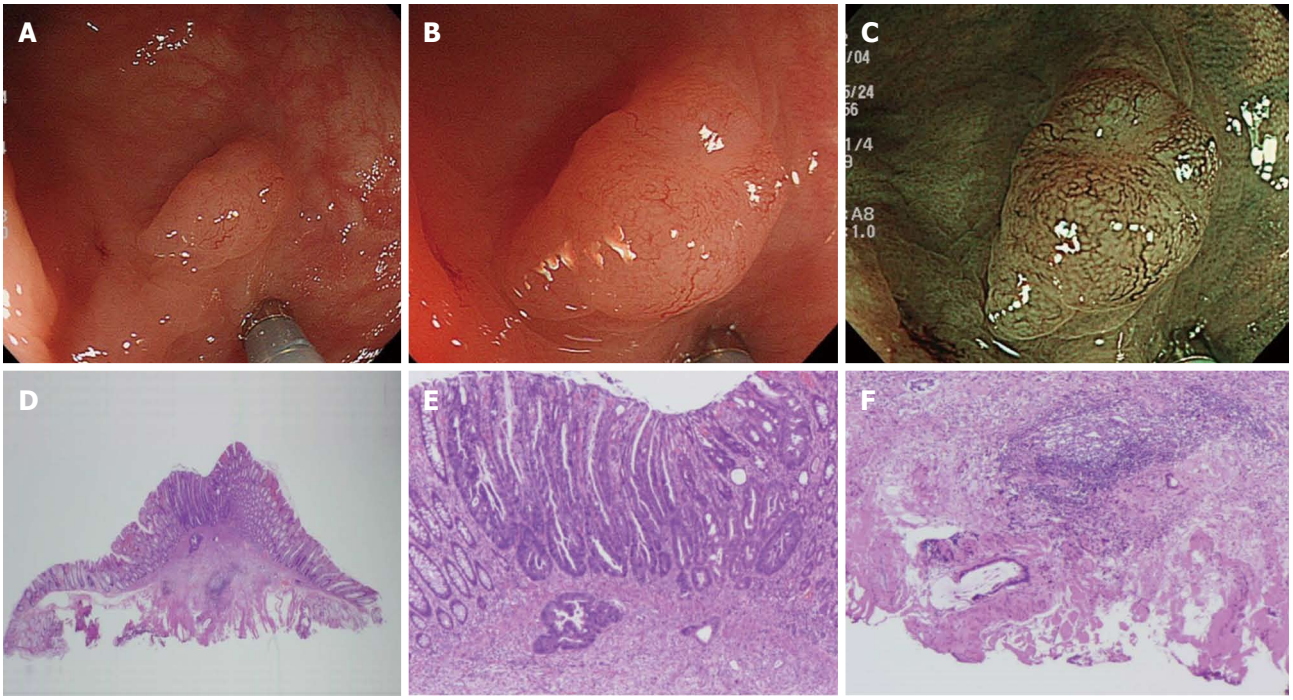

Figure 3 Invasive cancer 2 (S/C, 6 mm, Ⅱa + Ⅱc, Depressed type with NICE type 3). A and B: 0-Ⅱa + Ⅱc lesion was shown in sigmoid colon; C: NBI-magnifying endoscopy showed the feature classified as NICE type 3; D-F: Pathological diagnosis was well differentiated tubular adenocarcinoma with scirrhous growth, pSM-M, pVM(+), ly(+), v(+), budding grade 2-3.

Table 2 Clinicopathological feature

Total patient	468
Male/female	290/178
Mean age	66.3 (32-97, SD:)
Polyps	878
Mean size (mm)	4.7 (1-9, SD:)
Location (right side/left side)	542/336
Shape (pedunculated/sessile/flat/depressed)	12/274/590/2
Histology	
Non-neoplastic	123 (HP:100, SSA/P:13, other:10)
Adenoma	753 (TA:717, TVA:26, SA:10)
Grade (low/high)	711/42
Invasive cancer	2

HP: Hyperplastic polyp; SSA/P: Sessile serrated adenoma/polyp; TA: Tubular adenoma; TVA: Tubulovillous adenoma; SA: Serrated adenoma.

Table 3 Pathological evaluation using NICE classification

NICE classification	Non-neoplastic	Adenoma (low/high)	Invasive cancer
	Diminutive/small	Diminutive/small	Diminutive/small
NICE 1	42/12	11 (11/0)/9 (9/0)	0/0
NICE 2	63/6	564 (546/18) /169 (145/24)	0/0
NICE 3	0/0	0/0	1/1

NICE: NBI international colorectal endoscopic; Diminutive: 1-5 mm in diameter; Small: 6-9 mm in diameter.

NICE type 1 were adenomas with low-grade rather than high-grade atypia. The present data might suggest that the risk of failing to detect diminutive and small invasive colorectal cancers and that of leaving high-grade adenomas or intramucosal/SM scanty invasive carcinomas *in situ* with the "resect and discard" strategy could be avoided through the use of NBI observation with NICE classification and a magnifying endoscope.

The present study had some limitations. This was a single-center retrospective study and confidence levels were not determined. Further prospective research is required to validate the reliability of using the NICE classification with a magnifying endoscope in real-time colonoscopy.

In conclusion, the risk of failing to detect diminutive and small invasive colorectal cancers with the "resect and discard" strategy might be prevented by employing NICE classification under NBI magnification.

COMMENTS

Background

The "resect and discard" strategy offers costs savings benefits because it does not involve histological evaluation of tissue specimens; however, when discarding polyps without evaluating them histologically there is a risk of failure to detect invasive colorectal cancer.

Research frontiers

Recently, the NICE classification was proposed as a valid tool for not only differentiating hyperplastic from adenomatous polyps, but also predicting SM-d carcinomas in colorectal tumors. In the present study the authors aimed to assess the risk of failing to detect diminutive and small colorectal cancers in real-time using the "resect and discard" policy with NICE classification under narrow-band imaging (NBI) magnification.

Innovations and breakthroughs

Previous studies about the "resect and discard" strategy have reported that *in-vivo* optical diagnosis with high-definition white light followed by NBI without

magnification and chromoendoscopy seemed to be acceptable to assess polyp histopathology and future surveillance intervals. In the present study the authors innovated NICE classification and magnifying endoscopy to predict simply SM-d carcinomas among diminutive or small colorectal polyps.

Applications

The present data might suggest that the risk of failing to detect diminutive and small invasive colorectal cancers and that of leaving high-grade adenomas or intramucosal/SM scanty invasive carcinomas *in situ* with the "resect and discard" strategy might be prevented by employing NICE classification under NBI magnification.

Terminology

NICE classification is very simple and based on 3 characteristics including: (1) lesion color; (2) microvascular architecture; and (3) surface pattern, which consists of 3 types as shown in Table 1 and Figure 1.

Peer review

The paper proposes the "resect and discard" strategy of dimunitive and small polyps according their endoscopic features using NBI colonoscopes in conjunction with the NICE classification system.

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CLINICAL TRIALS STUDY

Comparison of split-dosing *vs* non-split (morning) dosing regimen for assessment of quality of bowel preparation for colonoscopy

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Author contributions: Shah H planned the study protocol and main write up of the article with screening of patients and assessing the bowel preparation; Desai D helped in write up of the article and screening of patients; Samant H and Davavala S helped in enrolling patients for the study and screening them; Joshi A, Gupta T and Abraham P valuable contribution for patient enrollment, screening and editing the article.

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Abstract

AIM: To compare (using the Ottawa Bowel Preparation Scale) the efficacy of split-dose *vs* morning administration of polyethylene glycol solution for colon cleansing in patients undergoing colonoscopy, and to assess the optimal preparation-to-colonoscopy interval.

METHODS: Single-centre, prospective, randomized, investigator-blind stud in an academic tertiary-care centre. Two hundred patients requiring elective colonoscopy were assigned to receive one of the two preparation regimens (split *vs* morning) prior to colonoscopy. Main outcome measurements were bowel preparation quality and patient tolerability.

RESULTS: Split-dose regimen resulted in better bowel preparation compared to morning regimen [Ottawa score mean 5.52 (SD 1.23) *vs* 6.02 (1.34); $P = 0.017$]. On subgroup analysis, for afternoon procedures, both the preparations were equally effective ($P = 0.756$). There was no difference in tolerability and compliance between the two regimens.

CONCLUSION: Overall, previous evening - same morning split-dosing regimen results in better bowel cleansing for colonoscopy compared to morning preparation. For afternoon procedures, both schedules are equally effective; morning preparation may be more convenient to the patient.

Key words: Bowel preparation; Colonoscopy; Morning preparation; Split dose preparation; Preparation to colonoscopy interval

Core tip: Split bowel reparation compared to single dose morning preparation resulted in a better bowel cleansing using the Ottawa Bowel Preparation Scale. The average score (± SD) using the Ottawa Scale was 6.02 ± 1.34 when morning preparation was given and 5.52 ± 1.23 when split preparation was given ($P = 0.017$). However, there was no statistical difference in the mean Ottawa score when the procedures were done in the afternoon with either the morning or the split preparation (6.09 *vs* 5.94, $P = 0.756$). Hence, AM only dosing is as effective as split dosing for patients scheduled for a colonoscopy in the afternoon.

Shah H, Desai D, Samant H, Davavala S, Joshi A, Gupta T, Abraham P. Comparison of split-dosing *vs* non-split (morning) dosing regimen for assessment of quality of bowel preparation for colonoscopy. *World J Gastrointest Endosc* 2014; 6(12): 606-611 Available from: URL: http://www.wjgnet.com/1948-5190/full/

v6/i12/606.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i12.606

INTRODUCTION

Successful completion of colonoscopy depends to a large extent on the quality of bowel preparation[1,2]. Poorly visualized mucosa leads to missed diagnoses and increases colonoscopic risk[3-5]. Even a small amount of residual stool can obscure small lesions such as angiodysplasia[5].

Bowel preparation has evolved from previous evening regimen to split dose regimen. Traditional colon preparation involves the unpleasant task of drinking a large volume of a cleansing solution the evening before the procedure. One way to increase tolerability and patient adherence is to split the dose so that the patient takes half the solution the evening before colonoscopy and the other half in the morning, usually about 4 to 5 h before the scheduled time of the procedure[6,7].

Prior studies have demonstrated that split dosing not only to improves patient acceptability, but also cleans the colon better[8]. Of 13 prospective, randomized studies done previously, 12 showed superior cleansing when whole or part of the bowel preparation was given in the morning of the scheduled colonoscopy[9-21].

However colonoscopies are often scheduled in the afternoon, and split dosing may not leave a clean colon by afternoon. A recent study by Matro *et al*[22] showing equal cleansing efficacy and tolerability of a morning dosing and split preparation when procedures are slated for the afternoon; this study did not include procedures scheduled in the morning.

The quality of bowel cleansing is generally assessed by the quantity of solid or liquid stool in the lumen. An adequate colonic examination is one that allows confidence that mass lesions other than small (< 5 mm) polyps not to be obscured by the preparation[23].

The primary aim of this study was to evaluate the efficacy of colon cleansing in patients undergoing colonoscopy, comparing the modality of administration, *i.e.*, split (previous eveningsame morning) *vs* morning-only dose, using the Ottawa Bowel Preparation Scale (Ottawa Scale)[24]. We also assessed how the time interval between the last dose of bowel preparation and the start of colonoscopy, *i.e.*, the preparation-to-colonoscopy (PC) interval, affects the quality of bowel preparation. The secondary aim was to study patient compliance and tolerability to the two preparation regimens and the willingness to repeat the bowel preparation in future if required.

MATERIALS AND METHODS

Patients seen in the outpatient clinic of our department as well as hospitalized patients who required elective colonoscopy were screened for enrolment in the study. Exclusion criteria included patients under 18 years of age, presence of severe renal impairment (creatinine clearance < 30 mL/min) or patients on haemodialysis, pregnant or lactating women, severe congestive heart failure (NYHA Ⅲ or Ⅳ), history of bowel obstruction or resection, known allergies to polyethylene glycol (PEG), and refusal of consent for the study. Patients who were inconvenienced by the timing of bowel preparation were also excluded. Approval from the hospital's ethics committee was obtained. Written, informed consent was obtained from each patient.

Patients were provided written instructions in a sealed opaque envelope, for either of the bowel preparations, by their gastroenterologists who were blinded to the content of the envelope. The envelopes were randomized in blocks of five (using a computer-generated random numbers table) by an independent study assistant who kept the randomization key under lock until the inclusion of the last patient. Investigator and colonoscopist were blinded to group allocation.

Bowel preparation

All patients were instructed to adhere to a liquid diet the day before their colonoscopy, and only clear liquids orally after midnight until the procedure time. The morning preparation group was instructed to consume one packet of PEG dissolved in 2 L of water on the morning of the colonoscopy (between 5 am and 7 am). The split-dose group was instructed to dissolve one packet of PEG in 2 L of water and consume one-half of this the evening before the day of the colonoscopy (between 6 pm and 7 pm) and the other half on the morning of the procedure (between 6 am and 7 am).

Patients were advised not to discuss their bowel preparation with their endoscopist but to contact the study assistant or the receiving nurse if questions arose. A mechanism was established to address patient concerns and issues of safety, without unblinding the endoscopist. They were given a questionnaire to be completed once their bowel preparation was finished and before coming to the hospital for the colonoscopy. The questionnaire included details about the tolerability of the regimen, compliance with the instructions for bowel preparation and diet, the amount of preparation taken, and completion time of the last PEG dose. Drinking at least 75% of the preparation volume was regarded as proper amount of PEG taken for bowel preparation. The following data were also collected: age, sex, indication for the procedure, history of abdominal or gynaecologic surgery, history of constipation, and other co-morbidities including diabetes, hypertension, and renal failure.

Colonoscopy

Colonoscopies were performed with the patients under conscious sedation by either a gastroenterology fellow or a consultant gastroenterologist. All colonoscopies were done between 11 am and 4 pm (morning sessions between 11 am and 1 pm, afternoon sessions between 1 pm and 4 pm). Time of completion of the last PEG dose and colonoscopy starting time were recorded, and

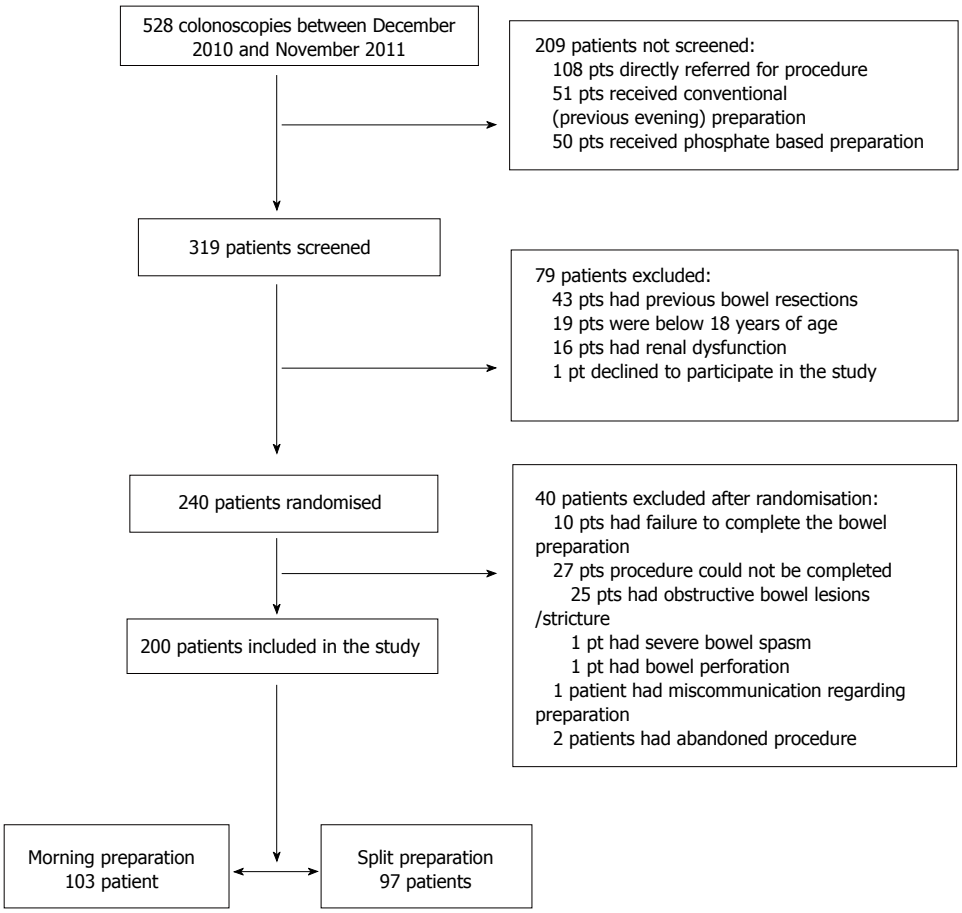

Figure 1 Study design: Group Randomisation.

the PC interval was calculated. A minimum of 4 h was kept between the completion of the last PEG dose and the start of colonoscopy for all patients.

A combination of intravenous fentanyl 50 mcg and midazolam 2 mg was used for sedation in patients in whom there was no contraindication; half the dose was used in patients over the age of 60 years. Additional sedation was used if required and permissible. Pulse, blood pressure, and oxygen saturation were measured in all patients before, during and after the procedure.

Bowel cleansing was evaluated by using the Ottawa Bowel Preparation Scale[24]. This scale assesses cleanliness and fluid volume separately. Cleanliness was assessed separately for the right colon (caecum, ascending), mid colon (transverse, descending), and the rectosigmoid on a 5-point scale (no liquid = 0, minimal liquid, no suctioning required = 1, suction required to see mucosa = 2, wash and suction = 3, solid stool, not washable = 4). Fluid quantity was rated from 0 to 2 for the entire colon (minimal = 0, moderate = 1, large = 2). The Ottawa Scale scores range from 0 (perfect) to 14 (completely unprepared colon). An excellent preparation would score 0 to 2; a good preparation, 3 to 5; and scores higher than 5 would indicate progressively worsening bowel preparation. A completely unprepared colon would score 11 to 14, depending on the amount of colonic fluid. The quality of preparation was assessed at the time of insertion of the colonoscope before any cleansing maneuvers. Each patient's colonoscopy was recorded on a DVD; the bowel-preparation quality was rated by a single investigator who was blinded to the type of preparation, and the results recorded on a standardized form.

Statistical analysis

On the basis of data from previous studies[20-22], a sample size of 200 patients was estimated to give an 80% power at a two-sided alpha of 0.05% to detect a 15% difference in the Ottawa bowel preparation quality scale. Bowel preparation scores measured by the Ottawa Scale were compared between the morning and split-dose groups using the Mann-Whitney *U* test. Pearson χ^2 test and continuity correction was used for comparing proportions in the two groups. A value of $P < 0.05$ was considered statistically significant.

RESULTS

In this prospective, randomized, investigator-blinded study, we enrolled 200 patients (mean age 51.8 years, SD 15.9, range 18-88; 121 men) between December 2010 and November 2011. A total of 528 colonoscopies were done during this period. Of these, 319 patients were screened for inclusion in the study. Screening was not possible

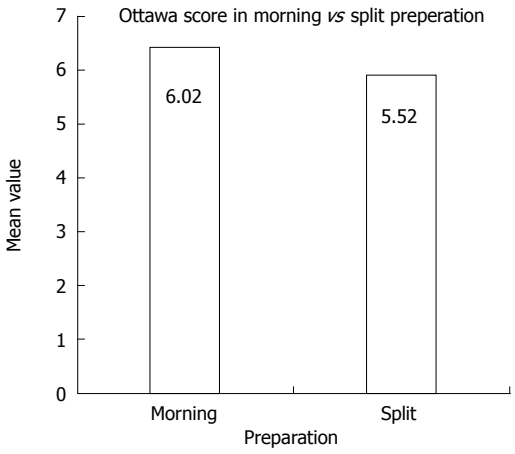

Figure 2 Comparison of morning and split preparation using Ottawa score.

in the remaining 209 patients-108 patients were directly referred for colonoscopy without being randomized, 51 were given the conventional previous-evening bowel preparation, and 50 took another bowel-preparation solution as advised by their referring physician. Of the 319 patients screened, 240 were randomized; 79 patients were excluded as they did not meet the inclusion criteria: previous bowel surgeries (n = 43), below age 18 years (19), renal dysfunction or on haemodialysis (16), and refusal of consent (1).

Of the 240 patients randomized, 40 were excluded: failure to complete bowel preparation as advised (n = 10; 6 in morning and 4 in split dose regimen); miscommunication regarding bowel preparation (1); inability to complete colonoscopy due to bowel lesion/stricture (25), spasm (1) and perforation (1). Two patients had extremely poor bowel preparation (both had taken morning preparation) and hence colonoscopy was abandoned and they were given a repeat bowel preparation.

Cecal intubation rate was 99.5% in our study. Only patients who had a complete colon examination from anal verge up to the cecum were included in the analysis. Of 200 such patients (109 outpatients, 91 inpatients), 103 received morning preparation and 97 received the split preparation (Figure 1). Total 135 patients underwent endoscopies in the morning (70 from morning preparation and 65 from split preparation). Both groups were comparable in terms of demographic data (62 males in morning preparation and 59 males in split preparation, median age = 53 years in both groups) and indications for colonoscopy.

Quality of bowel preparation

The split preparation had better bowel efficacy compared to the morning preparation. Overall, 88 (44%) patients had Ottawa score 5 or less indicating good bowel preparation. 93 (46.5%) had average bowel preparation with score 6 and 7, and 19 (9.5%) patients had poor bowel preparation with score above 8. The mean Ottawa Scale score (SD) was 6.02 (1.34) with the morning preparation and 5.52 (1.23) with split preparation (P = 0.017) (Figure 2). With morning colonoscopy (11 am-1 pm), the mean Ottawa score was 5.99 and 5.31 (P = 0.007) for the morning and split preparations, respectively. With afternoon colonoscopy, the corresponding scores were 6.09 and 5.94 (P = 0.756), respectively.

PC interval

A gap of at least 4 h was kept for every patient between the last preparation intake and the time of colonoscopy. Afternoon colonoscopies with PC interval > 6 h had poor bowel preparation (Ottawa score 5.66) compared to morning colonoscopies with PC interval between 4 and 6 h (6.02; P = 0.075).

Tolerability of the preparation and sleep disturbance

Nausea was complained of by 29.1% of patients with the morning preparation and 19.6% with split preparation (P = 0.161), abdominal discomfort by 9.7% and 13.4%, (P = 0.551), vomiting by 10.7% and 11.3% (P = 1.0), bloating by 12.6% and 9.3% (P = 0.597), and headache, dizziness and uneasiness by 4.9% and 4.1%, respectively (P = 1.0). Sleep was disturbed in 8 (7.8%) patients receiving the morning preparation and in 14 (14.4%) patients receiving the split preparation (P = 0.201). No patient experienced inconvenience while travelling.

DISCUSSION

Traditionally, the entire bowel-cleansing preparation solution is given in the evening prior to colonoscopy. In order to avoid sleep disturbance, it has to be given early in the evening. Alternatively, the preparation solution can be taken in a split dose, 8-12 h apart. Studies have shown that ingesting at least a part of the purgative on the day of colonoscopy and coordinating the final dose of purgative with the start time of colonoscopy is more likely to result in adequate colon cleansing[11,25]. Generally, this is accomplished by splitting the purgative between the evening prior and the morning of colonoscopy.

Previous studies have shown that the split preparation is better than the conventional previous-evening preparation in terms of bowel preparation quality and patient compliance[14,17,18,25,26]. The split-dose option is also endorsed by the American College of Gastroenterology and is considered an optimal choice for colonoscopy[27]. However, there have been few studies comparing split preparation to same-day morning preparation, which may be more convenient to patients as it does not interfere with common office schedules. We have shown earlier that same-morning preparation was better than previous-evening preparation[20]. In the present study we compared split dose with same-morning preparation.

In this study, split dosing resulted in better bowel cleansing than the same-morning preparation, both overall and when colonoscopy was performed in the morning. However, there was no difference in the mean

Ottawa score when colonoscopies were done in the afternoon. For patients scheduled for a colonoscopy in the afternoon, either of the preparation is comparable. The advantage of the morning preparation is it interferes less with the patient's routines and work schedules; patients often complain about trouble sleeping after taking the evening preparation.

A PC interval of 4 to 6 h resulted in better bowel preparation compared to one greater than 6 h. When patients were scheduled for the afternoon list, an interval between preparation and procedure greater than 6 h resulted in inferior bowel preparation, although this was not statistically significant. A long interval results in thick secretions emptying out of the small intestine and obscuring the caecum and ascending colon at the time of colonoscopy.

Seo *et al*[28] evaluated 366 consecutive outpatients undergoing colonoscopy using the split preparation; colonoscopies with PC interval 3 to 5 h had the best bowel preparation quality. Matro *et al*[22] compared the efficacy and tolerability of morning-only PEG to split-dose PEG for afternoon colonoscopy, and found both equivalent with respect to cleansing efficacy and polyp detection. Morning-only preparation was associated with lower incidence of abdominal pain, superior sleep quality, and less interference with work day prior to colonoscopy. While conventionally colonoscopies are performed in the morning, linking the administration of the preparation to the time of the procedure for both morning-only and split dosing may make late morning and afternoon colonoscopy equally attractive to patients.

In our study, there was no difference in tolerability between the morning and split regimens. Both regimens were equally well tolerated, with most patients willing to repeat the preparation in the future if the need arises.

In conclusion, split evening-morning dosing is superior to morning-only dosing for colon cleansing prior to colonoscopy if the procedure is slated in the morning; for afternoon colonoscopy, morning-only preparation is as effective. Optimal colon cleansing requires purgative administration close to the time of colonoscopy. For patients scheduled for colonoscopy in afternoon, it may be convenient to take the preparation in morning so that PC interval is minimized.

COMMENTS

Background

There is no standard recommendation regarding the timing of colonoscopy preparation. Different regimens are mentioned in literature. Traditionally, the entire preparatory solution is given in the evening, a day prior to the procedure. Alternatively, the preparatory solution can be taken in a split dose, 8-12 h apart. Studies have shown that ingesting at least a part of the purgative on the day of colonoscopy and coordinating the final dose of purgative with the start time of colonoscopy is more likely to result in adequate colon cleansing. Generally, this is accomplished by splitting the purgative between the evening prior and the morning of colonoscopy. Previous studies have proved that the split preparation is better than the conventional previous evening preparation in terms of bowel preparation quality and patient compliance. The split dose option is also endorsed by the American College of Gastroenterology and is considered an optimal choice for colonoscopy. But there have been very few studies comparing split preparation to same day morning preparation, which is more relevant to current clinical practice. What people looked at was can people administer the colon preparation the same day and get equal results? Is there a better way for bowel preparation without inconveniencing the patient? This rationale for the study was to compare the quality of bowel preparation using the same morning *vs* split regimens and also assess the importance of preparation-to-colonoscopy (PC) interval. The primary endpoint was whole colon preparation adequacy.

Research frontiers

Though there are several factors implicated in successful completion of a colonoscopy, quality of bowel preparation and timing of colonoscopy are considered two modifiable factors to improve successful completion. Improving the quality of colonoscopy is a major initiative of many digestive disease organizations. Various studies are ongoing to assess how the time interval between the last dose of bowel preparation and the start of colonoscopy, *i.e.*, the PC interval, affects the quality of bowel preparation and to determine the optimal PC interval for satisfactory bowel preparation.

Innovations and breakthroughs

Previous studies have proved that the split preparation is better than the conventional previous evening preparation in terms of bowel preparation quality and patient compliance. However, in this study there was no difference in the quality of bowel preparation for patients undergoing colonoscopy in afternoon with either the split or the same day morning preparation. Hence, same day bowel preparation should become a new standard for afternoon colonoscopy.

Applications

This study expands the options for patients by demonstrating that ingestion of polyethylene glycol preparation entirely on the day of colonoscopy is as good as a split dose schedule for an afternoon procedure.

Terminology

Split preparation: Where the patient takes half the laxative prescription the evening before colonoscopy and the other half in the morning of the scheduled procedure.

Peer review

The article entitled "Comparison of split-dosing *vs* non-split (morning) dosing regimen for assessment of quality of bowel preparation for colonoscopy" by Shah *et al* describes a study comparing the effect of morning-only and split bowel preparation of PEG solutions on bowel cleansing, for both morning and afternoon colonoscopies. Overall this study is timely and interesting to the readership.

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PROSPECTIVE STUDY

Small bowel ulcerative lesions are common in elderly NSAIDs users with peptic ulcer bleeding

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Abstract

AIM: To determine the frequency of small bowel ulcerative lesions in patients with peptic ulcer and define the significance of those lesions.

METHODS: In our prospective study, 60 consecutive elderly patients with upper gastrointestinal bleeding from a peptic ulceration (cases) and 60 matched patients with a non-bleeding peptic ulcer (controls) underwent small bowel capsule endoscopy, after a negative colonoscopy (compulsory in our institution). Controls were evaluated for non-bleeding indications. Known or suspected chronic inflammatory conditions and medication that could harm the gut were excluded. During capsule endoscopy, small bowel ulcerative lesions were counted thoroughly and classified according to Graham classification. Other small bowel lesions were also recorded. Peptic ulcer bleeding was controlled endoscopically, when adequate, proton pump inhibitors were started in both cases and controls, and *Helicobacter pylori* eradicated whenever present. Both cases and controls were followed up for a year. In case of bleeding recurrence upper gastrointestinal endoscopy was repeated and whenever it remained unexplained it was followed by repeat colonoscopy and capsule endoscopy.

RESULTS: Forty (67%) cases and 18 (30%) controls presented small bowel erosions (P = 0.0001), while 22 (37%) cases and 4 (8%) controls presented small bowel ulcers (P < 0.0001). Among non-steroidal anti-inflammatory drug (NSAID) consumers, 39 (95%) cases and 17 (33%) controls presented small bowel erosions (P < 0.0001), while 22 (55%) cases and 4 (10%) controls presented small bowel ulcers (P < 0.0001). Small bowel ulcerative lesions were infrequent among patients not consuming NSAIDs. Mean entry hemoglobin was 9.3 (SD = 1.4) g/dL in cases with small bowel ulcerative lesions and 10.5 (SD = 1.3) g/dL in those without (P = 0.002). Cases with small bowel ulcers necessitate more units of packed red blood cells. During their hospitalization, 6 (27%) cases with small bowel ulcers presented bleeding recurrence most possibly attributed to small bowel ulcers, nevertheless 30-d mortality was zero. Presence of chronic obstructive lung disease and diabetes was related with unexplained recurrence of hemorrhage in logistic regression analysis, while absence of small bowel ulcers was protective (relative risk 0.13, P = 0.05).

CONCLUSION: Among NSAID consumers, more bleeders than non-bleeders with peptic ulcers present small bowel ulcers; lesions related to more severe bleeding and unexplained episodes of bleeding recurrence.

Key words: Non-steroidal anti-inflammatory drugs; Aspirin; Wireless capsule endoscopy; Small bowel ulcerative lesions; Peptic ulcer bleeding

Core tip: Non-steroidal anti-inflammatory drugs (NSAIDs) can frequently cause small bowel ulcerative lesions. In our prospective case control study we found that 95% of elderly patients with peptic ulcer bleeding consuming NSAIDs also presented small bowel erosions and 55% small bowel ulcers. Small bowel ulcerative lesions were 3 times less frequent in patients with a non-bleeding peptic ulcer consuming NSAIDs, and infrequent among patients with a peptic ulcer not receiving NSAIDs. Small bowel ulcers in peptic ulcer bleeders were related with lower entry hemoglobin and increased need for blood transfusion. Moreover, they could be incriminated for unexplained bleeding recurrence despite successful peptic ulcer hemostasis.

Tsibouris P, Kalantzis C, Apostolopoulos P, Zalonis A, Isaacs PET, Hendrickse M, Alexandrakis G. Small bowel ulcerative lesions are common in elderly NSAIDs users with peptic ulcer bleeding. *World J Gastrointest Endosc* 2014; 6(12): 612-619 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i12/612.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i12.612

INTRODUCTION

Non-steroidal anti-inflammatory drug (NSAID) therapy reduces inflammation and pain very effectively[1], whilst low-dose aspirin is a common antithrombotic drug[2]. Benefits from NSAID use are offset by potentially life-threatening gastrointestinal complications[3-5]. NSAIDs can cause functional and structural small intestinal abnormalities[4,5]. The later could be accessed by either double-balloon[6] or capsule endoscopy (WCE)[1].

WCE identified small bowel mucosal damage (mucosal breaks, reddened folds, petechiae and denuded mucosa) in 50%-70% of healthy volunteers after a short course of NSAIDs and even more lesions in chronic NSAID consumers[1,7,8]. On the contrary mucosal damage was present only in 10% of subjects not exposed to NSAIDs[1]. Although small bowel mucosal lesions are frequent, they rarely produce small and large bowel complications[9]. Less than 1% of overt or obscure gastrointestinal bleeding cases can be attributed to small bowel ulcerative lesions[10]. Type of NSAID treatment (aspirin, non-aspirin NSAIDs) and patient age can increase the risk for a bleeding episode[11]. The role of a concurrent peptic ulcer is rather unknown.

In a small study, 90% of patients with a non-bleeding gastric ulcer receiving low dose aspirin also presented small bowel mucosal lesions[12]. A small pilot study in our department provided an indication that small bowel ulcerative lesions are even more frequent in peptic ulcer bleeders[13].

Our primary end-point was to determine the frequency of small bowel ulcerative lesions in patients with peptic ulcer bleeding compared to those with non-bleeding ulcers. While our secondary end-points were to determine: (1) whether NSAID use affects the frequency of small bowel lesions and (2) whether presence of small bowel lesions affects the severity of the bleeding episode and its' outcome.

MATERIALS AND METHODS

Patients-data

Our study was a prospective one. 60 consecutive patients older than 18 years, admitted in NIMTS Hospital (Military Insurance Fund Hospital) between the 1/1/2008 and 31/12/2009 with upper gastrointestinal bleeding due to a peptic ulcer entered the study (cases). None had a previous history of iron deficiency anemia. Each case was matched for age, gender, smoking, and alcohol consumption, to a non-bleeding ulcer patient (control) evaluated with WCE, between 1/1/2008 and 31/12/2012 in our department. Controls had WCE performed for chronic diarrhea or unexplained diffuse abdominal pain.

Upper gastrointestinal endoscopy was performed for each case within 24 h from admission and comprised hemostasis for Forrest I a, I b or II a ulcers[14]. For controls upper gastrointestinal endoscopy was performed before WCE study. During entry gastroscopy, *Helicobacter pylori* (*H. pylori*) infection was determined using rapid urease test and histology (haematoxylin-eosin and modified Giemsa). A negative colonoscopy was an inclusion prerequisite for both cases and controls. Colonoscopy was obligatory in our hospital for every case of gastrointestinal bleeding, regarded as alarm symptomatology not with-held by upper-endoscopy findings, because a significant percentage of patients with peptic ulcer might have a colonic pathology as well[15]. No case or control was on proton pump inhibitor or H-2 receptor blocker before the study period. Continuous *iv* infusion of pantoprazole 8 mg/h after a bolus of 40 mg was started after hemostasis for 48 h; switched thereafter to pantoprazole 40 mg *po* o.d. Cases not necessitating hemostasis and controls received pantoprazole 40 mg *po* o.d.

Hemoglobin levels were measured in every case on admission and daily thereafter until discharge. Hemoglobin drop on admission was calculated from a reference level of 14 g/dL.

Exclusion criteria were pregnancy, known or suspected complete or partial stenosis of the small intestine, gastric or intestinal surgery, established delayed gastric emptying or diabetic gastroparesis, history of, or active, malignancy, history of hypersensitivity to proton pump inhibitors and presence of any serious central nervous system, psychiatric, cardiovascular, respiratory, musculoskeletal, or intestinal disease preventing the performance of WCE. We also excluded patients with known or suspected small bowel inflammation, including Crohn's disease, spondyloarthropathy, and seronegative

athritides; patients with celiac disease and patients on medication that influence NSAID enteropathy[16] (biologicals, sulphasalazine, misoprostol, metronidazole and biphosphonates). No case or control had a systemic rheumatic disease or received anticoagulants. Alcohol intake was withheld during the study period.

Actual NSAIDs consumption (including self medication and defaults from prescribed drugs) was accessed before WCE using a life style and medication questionnaire[17]. We validated the questionnaire, applying it to 20 patients before study initiation (k-value = 0.81). Although we intended to record any NSAID consumption, we have considered NSAIDs consumers only those patients who had received even a single dose of NSAIDs the week preceded WCE study. Continuous NSAIDs consumption (both aspirin and non-aspirin) for up to 2 wk was recorded as short term, while longer-term use was considered long-term[1,7,8].

The study protocol has the approval of the Scientific Council of NIMTS Hospital, standing for Ethics Committee of NIMTS Hospital. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). All patients gave and signed written informed consent, before entering the study.

Capsule endoscopy

Both cases and controls underwent WCE within 4 d after upper gastrointestinal endoscopy and colonoscopy. WCE study (Given SB2 video capsule system; Given Imaging Ltd) was performed according to conventional procedures described elsewhere[10] and it was part of the investigation protocol.

Monitoring period was 9 h. A.Z. has initially gone through all videos and defined the second part of the duodenum. Two independent endoscopists (P. T. and C. K) with vast endoscopic experience separately reviewed all videos, starting video reading from the second part of the duodenum. Both had no information on patient clinical characteristics or presence of any gastric or duodenal bulb lesions. In case of investigator disagreement, a third blinded expert (P. A.) reviewed the findings with the purpose of reaching a consensus. Small bowel mucosal lesions were classified according to Graham *et al*[1]: category 0, normal; category 1, petechiae/red spots; category 2, 1-4 ulcerative lesions up to 5 mm (erosions); category 3, > 4 erosions; and category 4, larger ulcerative lesions. Because agreement between the two investigators was almost perfect (k-value = 0.84) for grade-3 and 4 lesions and fair (k-value = 0.28) for scarce red spots and petechiae and because grade-2 lesions could be found in normal subjects[1], we confined the analysis in grade-3 (erosions) and 4 (larger ulcers) lesions. Other pathologic findings, mainly lymphangiectasia, angiodysplasias and polypoid lesions/tumors were also reported.

Patients with any small bowel pathology undergone repeat capsule endoscopy study a year later. In the meanwhile, NSAID use was prevented; *H. pylori* infection eradicated and polypoid/submucosal lesions received relevant treatment.

To overcome relevant biases, both Head of the Department (G. A.), responsible for treatment decision and ward trainee doctors were unaware of WCE report, unless it was decisive to refer for surgical or endoscopic treatment.

Statistical analysis

Student's *t*-test was used to calculate the difference between the means. The chi-square test or Fisher's exact test was used for nonparametric data as appropriate. A $P < 0.05$ was considered to be statistically significant. We performed logistic regression analysis to access risk factors for unexplained bleeding recurrence. We included known risk factors for ulcer bleeding recurrence (old age, male gender, diabetes mellitus, body mass index and presence of chronic obstructive lung disease) as well as a possible risk factor, presence of small bowel ulcers. The magnitude of each association was expressed in terms of odds ratio and the corresponding 95% confidence interval.

Assuming that: (1) two thirds of patients with peptic ulcer consumed NSAIDs; (2) 30% of patients with no bleeding peptic ulcer consuming NSAIDs and 10% of those not consuming NSAIDs had > 4 erosions[9]; and (3) 90% of peptic ulcer bleeders, consuming NSAIDs and 10% of those not consuming NSAIDs had > 4 erosions[13]: we estimated that a sample size of 30 patients in each patient group was adequate to reach a study power of 90%. We doubled sample size to secure adequate subgroup analysis (aspirin, non-aspirin NSAIDs).

RESULTS

Patients

A duodenal ulcer was found in 38 (63%) cases and as many controls and a gastric ulcer in 32 (53%) cases and an equal number of controls. Both gastric and duodenal ulcers were present in 10 (17%) cases and 10 (17%) controls. 6 (10%) cases had bled from the gastric and 4 (7%) from the duodenal ulcer. Hemostasis was performed in 12 (20%) cases; 8 (13%) with a duodenal and 4 (7%) with a gastric ulcer. Thirty-two (53%) cases and as many controls were receiving NSAIDs short-term ($P = 1.00$), while 8 (13%) cases and as many controls were on NSAIDs long-term ($P = 1.00$). There was no difference between cases and controls in any demographic or disease related characteristic, apart from diffuse abdominal pain that was more frequent among controls (Table 1). No case or control had chronic renal failure, liver failure or cirrhosis and none was receiving anticoagulants.

Findings in capsule endoscopy

Small bowel ulcerative lesions were found in 40 (67%)

Table 1 Demographic and disease related characteristics of bleeders and controls

Characteristic	Patients (n = 60)	Controls (n = 60)	P
Mean age (yr)	75 (SD = 8)	74 (SD = 9)	0.26
Male gender	44 (73%)	44 (73%)	1.00
Active smoking	18 (30%)	18 (30%)	1.00
Alcohol abuse	12 (20%)	12 (20%)	1.00
BMI > 25	36 (60%)	36 (60%)	1.00
NSAIDs consumption	40 (67%)	40 (67%)	1.00
Ischaemic heart disease	20 (33%)	20 (33%)	1.00
Chronic pain	6 (10%)	22 (37%)	0.006
Diabetes melitus	11 (18%)	12 (20%)	0.82
COPD	4 (7%)	4 (7%)	1.00
Low dose aspirin use[1]	22 (37%)	22 (37%)	1.00
Non aspirin NSAIDs use[1]	24 (40%)	24 (40%)	1.00
COX-2 selective use	6 (10%)	6 (10%)	1.00
Non selective NSAIDs use	18 (30%)	18 (30%)	1.00
Clopidogrel co-administration	12 (20%)	12 (20%)	1.00
Gastric passing time (min)	41 (SD = 49)	42 (SD = 57)	0.46
Small bowel passing time (min)	221 (SD = 117)	271 (SD = 117)	0.01
H. pylori positive	37 (60%)	37 (62%)	1.00

[1]Three bleeders and 6 controls received both low-dose aspirin and non-aspirin NSAIDs. SD: Standard deviation; NSAIDs: Non-steroidal anti-inflammatory drugs; BMI: Body mass index; COPD: Chronic obstructive lung disease; COX-2 selective use: Cyclooxygenase-2 selective inhibitors.

cases and 18 (30%) controls (P = 0.0001). All of them had erosions (grade-3 lesions), while small bowel ulcers (grade-4 lesions) were found 22 cases (37%) and 4 (8%) controls (P = 0.0001). Small bowel erosions were found in 27 (71%) cases with a duodenal and 20 (62%) with a gastric ulcer (P = 0.45), while small bowel ulcers were found in 16 (42%) cases with a duodenal and 10 (31%) with a gastric ulcer (P = 0.35). Moreover erosions were found in 14 (37%) controls with a duodenal and 9 (28%) with a gastric ulcer (P = 0.44), while small bowel ulcers were found in 3 (8%) controls with a duodenal and 2 (6%) with a gastric ulcer (P = 0.79).

Among NSAID consumers, 39 (98%) cases and 17 (43%) controls presented small bowel ulcerative lesions (P < 0.0001). All of them had small bowel erosions, while small bowel ulcers were present in 22 (55%) cases and 4 (10%) controls (P < 0.0001). Small bowel erosions were found in 26 (96%) cases with a duodenal and 20 (100%) with a gastric ulcer (P = 0.38), while larger ulcerative lesions were found in 16 (100%) cases with a duodenal and 10 (100%) with a gastric ulcer (P = 1.00). Moreover erosions were found in 13 (48%) controls with a duodenal and 9 (45%) with a gastric ulcer (P = 0.83), while larger ulcerative lesions were found in 3 (11%) controls with a duodenal and 2 (10%) with a gastric ulcer (P = 0.90).

There was no difference in small bowel mucosal lesions between cases and controls consuming no NSAIDs (Table 2). All cases and controls with small bowel erosions reporting no NSAID consumption admitted that they had received at least a single NSAID dose more than a week before WCE.

Among NSAID consumers, cases presented more small bowel erosions than controls both in the jejunum and the in the ileum (Table 3).

Small bowel erosions were present in 31 (97%) cases receiving NSAIDs long-term and 8 (100%) short-term

Table 2 Small bowel mucosal lesions found during video capsule endoscopy in both bleeders and controls

Patient group	Cases	Controls	P
All patients	n = 60	n = 60	
Grade 4 lesions	22 (37%)	4 (8%)	0.0001
Grade 3 lesions	40 (67%)	18 (30%)	0.0001
Grade 2 lesions	41 (68%)	21 (35%)	0.0003
Grade 1 lesions	42 (70%)	28 (47%)	0.0100
NSAID consumers	n = 40	n = 40	
Grade 4 lesions	22 (55%)	4 (10%)	< 0.0001
Grade 3 lesions	39 (95%)	17 (33%)	< 0.0001
Grade 2 lesions	40 (100%)	20 (50%)	< 0.0001
Grade 1 lesions	40 (100%)	26 (65%)	< 0.0001
No-NSAID consumers	n = 20	n = 20	
Grade 4 lesions	0	0	
Grade 3 lesions	1 (5%)	1 (5%)	1.00
Grade 2 lesions	1 (5%)	1 (5%)	1.00
Grade 1 lesions	2 (10%)	2 (10%)	1.00

NSAIDs: Non-steroidal anti-inflammatory drugs.

Table 3 Number of mucosal lesions found during video capsule endoscopy in both bleeders and controls consuming non-steroidal anti-inflammatory drugs, after stratification according to the type of non-steroidal anti-inflammatory drug consumed

Patient group	Patients	Controls	P
All patients	n = 40	n = 40	
Jejunum			
Grade 4 lesions	1 (SD = 2)	0.3 (SD = 0.7)	0.02
Grade 3 lesions	10.8 (SD = 4.3)	1 (SD = 0.6)	< 0.0001
Ileum			
Grade 4 lesions	1.1 (SD = 1.9)	0.2 (SD = 0.3)	0.002
Grade 3 lesions	8.1 (SD = 4.8)	1.2 (SD = 2.2)	< 0.0001
Low dose aspirin users	n = 22	n = 22	
Jejunum			
Grade 4 lesions	0.8 (SD = 1.3)	0.2 (SD = 0.4)	0.02
Grade 3 lesions	9.9 (SD = 4.7)	0.8 (SD = 0.5)	< 0.0001
Ileum			
Grade 4 lesions	0.9 (SD = 1.4)	0.1 (SD = 0.3)	0.006
Grade 3 lesions	10.3 (SD = 4.6)	1 (SD = 1.6)	< 0.0001
Non-aspirin NSAID consumers	n = 24	n = 24	
Jejunum			
Grade 4 lesions	1.4 (SD = 2.6)	0.4 (SD = 0.9)	0.04
Grade 3 lesions	11.9 (SD = 3.8)	1.2 (SD = 0.7)	< 0.0001
Ileum			
Grade 4 lesions	1.6 (SD = 2.4)	0.3 (SD = 0.3)	0.02
Grade 3 lesions	7.7 (SD = 4.8)	1.4 (SD = 2.3)	< 0.0001
COX-2 NSAID consumers	n = 6	n = 6	
Jejunum			
Grade 4 lesions	0.3 (SD = 0.6)	0	0.27
Grade 3 lesions	5.7 (SD = 6.7)	0.4 (SD = 1.4)	0.04
Ileum			
Grade 4 lesions	0.7 (SD = 1.2)	0	0.15
Grade 3 lesions	6.7 (SD = 5.7)	0.5 (SD = 0.7)	0.01

NSAIDs: Non-steroidal anti-inflammatory drugs; SD: Standard deviation; COX-2: Cyclooxygenase-2 selective inhibitors.

Table 4 Logistic regression analysis of demographic characteristics and co-morbidities related to a hemorrhage recurrence possibly related to the small bowel

Characteristic	Relative risk	Confidence intervals	*P*
Age	1.03	0.96-1.10	0.40
Male gender	3.63	0.61-21.46	0.15
Body mass index	1.22	0.90-1.63	0.19
Diabetes	2.14	1.35-3.40	0.001
Chronic obstructive lung disease	6.67	1.01-46.3	0.05
Absence of small bowel ulcers	0.13	0.01-0.99	0.05

(P = 0.61), while larger ulcerative lesions were found in 19 (59%) cases consuming NSAIDs long-term and 3 (38%) consuming them short-term (P = 0.27). On the other hand, small bowel erosions were found in 15 (47%) controls consuming NSAIDs long-term and 3 short-term (38%, P = 0.63); while small bowel ulcers were found in 3 (9%) controls consuming NSAIDs long-term and 1 long-term (13%, P = 0.79).

Twenty-four (67%) H. *pylori* positive and 15 (63%) negative cases (P = 0.74), as well as 11 (31%) H. *pylori* positive and 7 (29%) negative controls (P = 0.91) presented small bowel ulcerative lesions.

Small bowel ulcerative lesions were present in all cases (n = 16) and 1 (5%) control consuming low-dose aspirin only (P < 0.0001); 14 (78%) cases and 2 (9%) controls receiving non-aspirin NSAIDs only (P = 0.0001); 5 cases (83%) and 2 (33%) controls receiving both types of NSAIDs (P = 0.08). 4 (67%) cases receiving cyclooxygenase-2 selective inhibitors and one (16%) control presented small bowel erosions (P = 0.08), while larger lesions presented only in 2 (33%) cases (P = 0.12).

There was no difference between the two groups concerning presence of angiodysplasias [24 (40%) cases *vs* 25 (42%) controls, P = 0.85] and polypoid/submucosal lesions [2 (3%) cases *vs* 2 (3%) controls, P = 1.00].

Clinical course of peptic ulcer hemorrhage

Mean entry hemoglobin was 9.3 (SD = 1.4) g/dL in cases with grade-3 or 4 lesions and 10.5 (SD = 1.3) g/dL in those without (P = 0.002). It was 9.9 (SD = 1.5) g/dL in cases with small bowel erosions and 8.6 g/dL (SD = 1.2) in those with larger ulcerative lesions (P = 0.002). Thus calculated hemoglobin drop due to the bleeding episode was 4.7 g/dL in cases with grade 3 or 4 lesions and 3.5 g/dL in cases without ulcerative lesions (P = 0.001).

Cases with small bowel ulcerative lesions necessitated transfusion of 2.8 (SD = 1.2) units of packed red blood cells units while those without 1.1 (SD = 0.6, P < 0.0001). In addition, cases with small bowel ulcers necessitated transfusion of 3.9 (SD = 1.3) packed red blood cells units, while those with small bowel erosions 1.7 (SD = 0.9, P < 0.0001).

After admission and despite successful hemostasis, 7 (32%) cases with small bowel ulcers and none without presented a drop of hemoglobin > 2 g/dL (P = 0.05). Repeat upper gastrointestinal endoscopy revealed peptic ulcer rebleeding in one of them followed by repeat hemostasis, while repeat colonoscopy was negative. In repeat WCE study (because balloon enteroscopy was not available in the country), the remaining patients had at least one small bowel ulcer with a visible vessel on ulcer base with (n = 2) or without active bleeding (n = 4). Five (83%) bleeding recurrences that could possibly attributed to small bowel lesions were mild and self-limited. Nevertheless, one case necessitated operative small bowel endoscopy and hemostasis.

Logistic regression analysis, revealed that presence of diabetes mellitus and chronic obstructive lung disease were independent risk factors for bleeding recurrence possibly attributed to the small bowel, while absence of small bowel ulcers were protective (Table 4).

Thirty-day mortality was zero for both cases and controls and none reported any adverse event related to medical treatment or WCE.

Repeat capsule endoscopy a year later, revealed no ulcerative lesion in patients with small bowel ulcerative lesions in the entry endoscopy, providing that they had stopped NSAIDs during follow-up.

DISCUSSION

In our prospective case control study we found that 95% of elderly patients with peptic ulcer bleeding consuming NSAIDs presented small bowel erosions and 55% small bowel ulcers. Moreover, 30% of patients with a non-bleeding peptic ulcer consuming NSAIDs had small bowel erosions and 10% small bowel ulcers. Absence of small bowel ulcerative lesions was recorded in patients with peptic ulcer not receiving any NSAIDs. Small bowel ulcerative lesions in peptic ulcer bleeders were related with lower entry hemoglobin and increased need for blood transfusion. Finally, one out of four small bowel ulcers could bleed during the convalescence period of peptic ulcer bleeding leading to unexplained hemoglobin drop or even melena.

Our study has a number of limitations. It was conducted in a relatively limited number of rather old subjects; the vast majority of whom consumed NSAIDs chronically, while rheumatic disease was excluded. Thus although we included one of the main target groups of NSAID treatment, the elderly, we excluded the other, patients with rheumatic diseases[1]. Our study population old age was a result of reference bias, because our hospital is mainly a Veterans Hospital and referrals from secondary Hospitals usually exclude very young patients. More bowel ulcerative lesions are expected in the elderly because their large[18] and small bowel[19] is more vulnerable to NSAIDs. Patients with rheumatic diseases were excluded because rheumatoid artritis can cause small bowel ulcerative lesions in the absence of NSAID consumption[20]. Rheumatoid arthritis has been related to an increased frequency of iron deficiency anemia[21] and small bowel ulcerative lesions[20], among NSAIDs consumers, but no overt bleeding episodes[21]. Sample size although marginally adequate to explore the role of

aspirin and non-selective NSAIDs, it was insufficient to study the effect of cyclooxygenase-2 selective inhibitors. Proton pump inhibitors were given to all study subjects, a common practice when the study was conducted. Nevertheless recent reports suggest that proton pump inhibitors could exacerbate small bowel ulcerative lesions[22].

Small bowel ulcerative lesions are more frequent in reports including chronic NSAID consumers[1,23] than those including healthy volunteers who received NSAIDs short-term[8,23-26]. A head to head comparison in our study revealed no difference between short and long-term NSAID consumers with concurrent peptic ulcer. Thus, some kind of mucosal adaptation, such as heme oxygenase-1 up regulation[27], could have balanced NSAIDs deleterious effect over time[1].

Small bowel injury and clinically relevant complications associated with the use of NSAIDs, even small dose aspirin, are well recognized[23,25-27]. Nevertheless data on peptic ulcer patients are limited[12]. In our study, prevalence of small bowel ulcerative lesions in NSAID users with non-bleeding peptic ulcer equals the mean of medical literature for non-ulcer NSAIDs consumers[1,23,25-27], even that reported by our group for NSAID consumers with iron deficiency anemia[13]. On the contrary, prevalence of small bowel ulcerative lesions was much higher among NSAID consumers with peptic ulcer bleeding. High prevalence of small bowel mucosal lesions in peptic ulcer bleeders receiving NSAIDs could attributed either to a genetically determined susceptibility for mucosal damage[12] or to an alternated NSAID metabolism due to different CYP2C9 polymorphism[28]. Small bowel ulcerative lesions were 15% more frequent in our study than in Watanabe *et al*[12] report, a small study on 11 non-bleeding gastric ulcer patients receiving low-dose aspirin and proton pump inhibitors. The difference could be attributed to the younger age of Watanabe *et al*[19] patients and the use of low dose aspirin, a less toxic NSAID[11,27]. Inclusion of patients with duodenal ulcer, in our study, could not influence the final outcome, as we found no difference between gastric and duodenal ulcer patients.

Although small bowel mucosal lesions are frequent, small and large bowel complications are infrequent[29], but increase with the exposure to NSAIDs use[9]. Presence of small bowel ulcerative lesions in our non-bleeding ulcer patients was rather indolent, while small bowel ulcers could possibly related to obscure bleeding recurrence in peptic ulcer bleeders. Small bowel ulcers were rather infrequent found in 5%-25% of NSAID consumers[1,23,25-27], but 55% of peptic ulcer bleeders. The probability of small bowel lesions responsible for gastrointestinal bleeding beyond gastric/duodenal ulcers states that we should consider WCE in patients with persistent hemorrhage or bleeding recurrence and negative or inconclusive gastroscopy.

Balloon enteroscopy would have been a preferable option for unexplained bleeding recurrence episodes since it also holds therapeutic capabilities[30]. Nevertheless it was not available in our country during most of the study period.

Gastrointestinal bleeding episodes in NSAID consumers characterized by more severe blood loss and need for more transfusions[31,32], due to co-existence of various co-morbidities and bleeding time prolongation as a result of the antiplatelet effect of NSAIDs[32]. Our study pointed out that small bowel ulcerative lesions could be also important. Old age[33,34], obesity[33,35], presence of diabetes mellitus[35] and chronic obstructive lung disease[33,36] are risk factors for peptic ulcer rebleeding after successful hemostasis because they favor microcirculatory disturbances. Although numbers are too small to draw safe conclusions, our study speculated that presence of diabetes mellitus and chronic obstructive lung disease are important for bleeding recurrence due to small bowel lesions.

In conclusion, more than half patients with peptic ulcer bleeding who consume NSAIDs presented small bowel ulcers. Those lesions were related to lower entry hemoglobin, increased need for blood transfusion and possibly unexplained episodes of bleeding recurrence. Despite study limitations, the results provide a compelling argument for the design of further large-scale studies to define the extent of this potential problem, unravel the mechanisms determining a worse prognosis of patients with peptic ulcer bleeding due to NSAID use and develop strategies to treat small bowel lesions in addition to peptic ulceration.

COMMENTS

Background

Non-steroidal anti-inflammatory drugs are very effectively painkillers, while low-dose aspirin is a common antithrombotic drug. Nevertheless they have been incriminated for causing gastric and duodenal ulcers and their complications, the most common of which is bleeding. Non-steroidal anti-inflammatory drugs can also harm the small bowel. Although small bowel lesions are very common their significance is poorly defined.

Research frontiers

There are very few data pointing out that small bowel ulcers might be very common in patients with gastric ulcers receiving non-steroidal anti-inflammatory drugs. Also it seems that patients receiving non-steroidal anti-inflammatory drugs lose more blood and do worse when they bleed. The explanation given today is that their blood is thinner or that they suffer more co-morbidities, such as heart disease, stroke, lung or kidney diseases.

Innovations and breakthroughs

The authors have found that small bowel ulcers are more common in patients with a gastric or a duodenal ulcer receiving non-steroidal anti-inflammatory drugs and presenting with bleeding than those without bleeding. The authors have also found no small bowel ulcers in patients not receiving non-steroidal anti-inflammatory drugs. The ulcer bug does not affect the possibility to develop small bowel lesions. The authors have shown that small bowel ulcers in patients with bleeding that receive non-steroidal anti-inflammatory drugs mean greater blood loss and need for more transfusions. Final the authors found that in patients with a bleeding from a gastric or a duodenal ulcer that receive non-steroidal anti-inflammatory drugs can relapse not only from their gastric or duodenal ulcer but also from a small bowel ulcer.

Applications

The probability of small bowel lesions responsible for bleeding beyond gastric/duodenal ulcers states that the authors should consider pill camera gut investigation in patients with persistent bleeding or bleeding recurrence and

negative or inconclusive gastroscopy.

Terminology

A gastric or a duodenal ulcer represents a wound in the lining of the stomach or the beginning of the small bowel. The most common causes are the ulcer bug and non-steroidal anti-inflammatory drugs.

Peer review

It is an interesting work.

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CASE REPORT

Novel endoscopic management for pancreatic pseudocyst with fistula to the common bile duct

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Abstract

Pancreatic pseudocyst formation is a well-known complication of pancreatitis. It represents about 75% of the cystic lesions of the pancreas and might be located within or surrounding the pancreatic tissue. Sixty percent of the occurrences resolve spontaneously and only persistent, symptomatic or complicated cysts need to be treated. Complications include infection, hemorrhage, gastric outlet obstruction, splenic infarction and rupture. The formation of fistulas to other viscera is rare and most commonly occurs within the stomach, duodenum or colon. We report a case of a patient with a pancreatic pseudocyst in communication with the common bile duct. There have been only few cases reported in the literature. We successfully managed our case by performing an endoscopic ultrasound-guided drainage of the pancreatic collection and a contemporaneous stenting of the common bile duct. Performed independently, both drainages are effective, safe and well-coded and the expertise on these procedures is widespread. By our knowledge this therapeutic approach was never reported in literature but we retain this is the most correct treatment for this very rare condition.

Key words: Pancreatic pseudocyst; Fistula; Common bile duct; Endoscopic retrograde cholangiopancreatography; Endoscopic ultrasound

Core tip: In our opinion the combination of endoscopic ultrasound-guided drainage of the pseudocyst and the simultaneous biliary stenting represent the best endoscopic treatment. The advantages of such approach consist in a better evaluation and a more effective drainage of the cystic cavity with the possibility to collect samples for biochemical and bacteriological analysis. Furthermore, the simultaneous biliary stenting can determine, at the same time, a pressure reduction in the bile system and in the pancreatic collection facilitating the healing of the fistula.

Crinò SF, Scalisi G, Consolo P, Varvara D, Bottari A, Pantè S, Pallio S. Novel endoscopic management for pancreatic pseudocyst with fistula to the common bile duct. *World J Gastrointest Endosc* 2014; 6(12): 620-624 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i12/620.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i12.620

INTRODUCTION

Pancreatic fluid collections (PFCs) arise from disruption of a pancreatic duct, with leakage of pancreatic juice

into the surrounding peripancreatic tissues, and comprise about 75% of the cystic lesions of the pancreas[1].

The revised Atlanta classification refers to collections within 4 wk of symptom onset as either acute peripancreatic fluid collections or postnecrotic pancreatic fluid collections depending upon the absence or presence of pancreatic/peripancreatic necrosis, respectively. After 4 wk of the onset of symptoms, persistent collections may gradually develop a fibrous walls and are referred to as pseudocysts (PPs) or walled-off necrosis, again depending upon the absence or presence of necrosis, respectively. In addition, these collections are further classified as sterile or infected[2].

PPs occur as a complication of acute pancreatitis in approximately 10%-20% of cases. Most of these resolve spontaneously[3] and size and duration have not been shown to be the predictors of morbidity and mortality. Expectant management even in asymptomatic large PPs has shown favorable results.

Intervention is only required in patients who develop symptoms[4] such as abdominal pain, mechanical obstruction of the gastric outlet with nausea or vomiting, jaundice for compression of the biliary system, or in whom an infection is suspected for the effective control of sepsis[5].

In recent years, it has gradually been recognized that, due to its lower morbidity rate compared to the surgical and percutaneous approaches, endoscopic treatment may be the preferred first-line approach for managing PFCs[6]. Endoscopic ultrasound (EUS)-guided drainage became the preferred method of draining PFCs which lie within 1 cm of the gastric or duodenal wall, because it presents several advantages: (1) EUS can distinguish PFCs from cystic tumors, the gallbladder and pseudoaneurysm; (2) EUS can determine the content of the PFC, such as if significant necrotic debris is present, which would then require more aggressive endoscopic approach; (3) EUS can identify interposed blood vessels and potentially reduce the risk of bleeding; and (4) EUS permits drainage of non-bulging PFCs[7].

Complications of PPs are uncommon and include sepsis, hemorrhage or pseudoaneurysm formation, rupture with pancreatic ascites, and, rarely, fistula formation to other viscera[8].

The most common sites for fistulas are between PPs and stomach, duodenum, colon and, less commonly, esophagus. Fistulas usually cause pain, inflammation, fever, septicemia, and compression of neighboring structures[9].

Fistulous communication of PPs to the common bile duct (CBD) is uncommon. It affects more frequently males, most common etiology is alcoholic chronic pancreatitis and abdominal pain is the main clinical presentation. To the best of our knowledge, there have been 17 cases reported in the literature[10-23], only three of which managed endoscopically[21-23]. We present a case of this rare condition successfully resolved performing a simultaneous, independent drainage of the PPs and the CBD, never reported in literature.

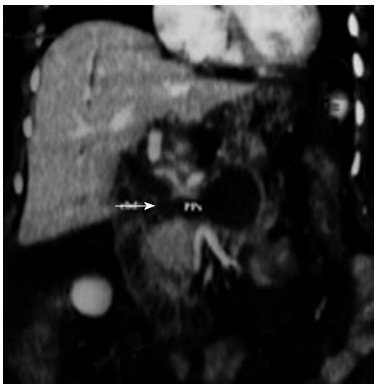

Figure 1 Coronal computed tomography reconstruction showed a large pancreatic pseudocyst with a fistulous communication (arrow) to the common bile duct.

CASE REPORT

Here we describe the case of a 67-year-old Caucasian woman with history of gallstones. She didn't refer alcohol abuse, use of drugs or history of hypertriglyceridemia. She was firstly admitted in our hospital for the onset of acute severe pancreatitis with pancreatic necrosis and acute peripancreatic fluid collection. Ranson score after 48 h was 4. She was managed conservatively and discharged after 4 wk, for the onset of concurrent nosocomial infection (pneumonia). Two weeks later, she developed progressive jaundice, upper quadrants abdominal pain and fever. Laboratory investigation revealed leukocytosis (WBC 20700) and increased indices of cholestasis. Abdominal contrast-enhanced computed tomography (CT) scan (Figure 1) showed in the region of the pancreatic head an 8 cm × 3 cm PPs in communication with the CBD that was dilated (12 mm) such as the intrahepatic bile ducts. Pancreatic duct was normal. Subsequently, the patient underwent endoscopic retrograde cholangiopancreatography (ERCP) that revealed a long, distal biliary extrinsic compression and confirmed a fistulous communication between middle tract of the CBD and large PPs in the head of the pancreas. Biliary sphincterotomy was performed and a 10 Fr × 7 cm plastic stent was placed in the CBD.

The duodenoscope was switched for an echoendoscope: at EUS the PPs resulted relatively thin-walled, with optimal contact with the gastric wall, within abundant echoic debris and encompassing both splenic vessels. Doppler assessment excluded large vessels interposition and EUS-guided drainage was performed. A 19-gauge dedicated needle (ECHO-HD-19-A, Wilson-Cook Medical Inc., Winston-Salem, North Carolina, United States) was used for the puncture of the collection (Figure 2A) and brown-purulent fluid was aspirated for bacteriological examination. A first 0.035-inch guidewire (Jagwire; Microvasive Endoscopy, Boston Scientific Corp., Natick, Massachusetts, United States) was advanced

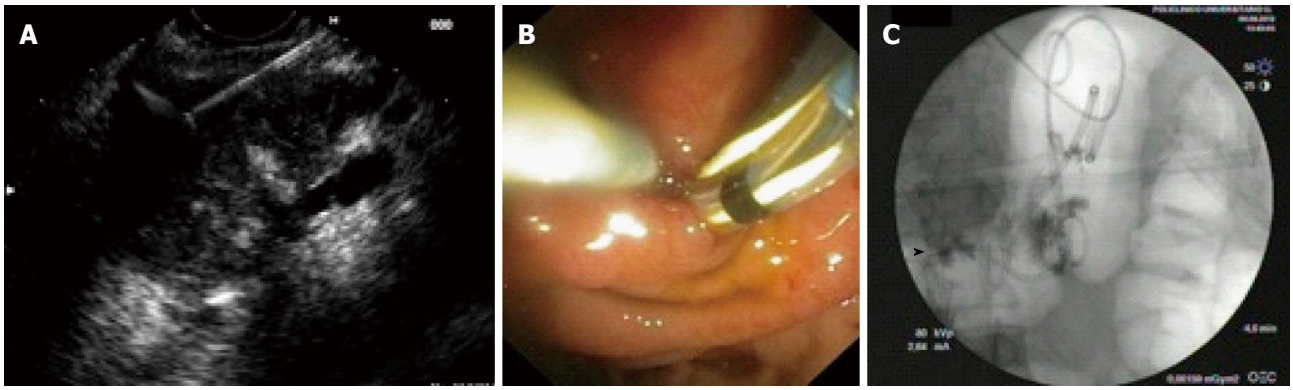

Figure 2 Pancreatic pseudocystis intervention. First step: Endoscopic ultrasound-guided puncture with 19-gauge dedicated needle of the pancreatic collection containing necrotic debris (A); Second step: Placement of the first plastic stent and two guidewire into the pseudocysts (PPs) for the placement of the second stent and the nasocystic drain (B); Third step: Fluoroscopic image showing the biliary stent (arrowhead), two PPs double pigtail stents and the nasocystic drain (C).

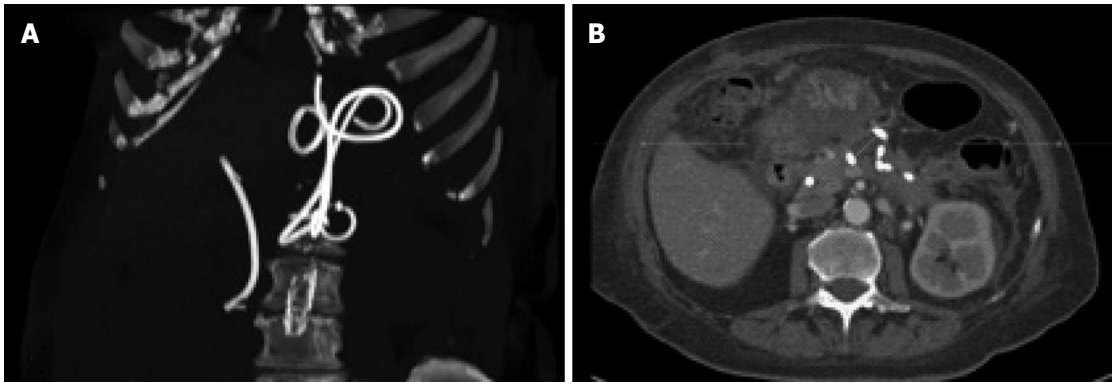

Figure 3 Computed tomography scan performed three weeks later: Scan reconstruction showing the correct position of the biliary and pancreatic collection stents (A), while the axial scan show almost complete resolution of the cystic cavity (B).

into the PPs through the inner part of the needle under fluoroscopic guidance and dilation of the fistula was obtained using a 8 mm biliary dilation balloon over the guidewire. After placing a first 10 Fr × 6 cm double pigtail plastic stent, two more 0.035-inch guidewires were placed into the collection through a catheter (Figure 2B) and a second 10 Fr double pigtail stent and a 7 Fr nasocystic catheter were then inserted (Figure 2C).

Bacterial culture from the pancreatic fluid collection resulted positive for Klebsiella Pneumonie. The patient was started on antibiotics and daily collection aspiration and washing was performed trough the nasocystic drainage. After 5 d the patient was in good clinical condition and was discharged and scheduled for the follow up. Three weeks later CT scan showed the correct position of the biliary and cystic stents (Figure 3A) and revealed a quite complete reduction of the cystic cavity (Figure 3B); the nasocystic drain was than removed.

Three months later, ERCP was performed for removing the biliary stent: cholangiography revealed, after high-pressure contrast injection with a balloon catheter, the resolution of the biliary fistula (Figure 4). Both double pigtail plastic stents were leaved in place in the stomach and removed only after a further 6 mo follow up. Patient was followed for 8 mo without evidence of recurrence of the pseudocyst.

DISCUSSION

Fistulous communication of PFCs to the CBD is distinctly rare. Clinical symptoms, as in our case, are generally right upper quadrant abdominal pain, jaundice and fever.

Management of this rare condition is not defined and, in literature, only seventeen cases have been reported, ten of whom were treated surgically, three with percutaneous external drainage and one was observed. Only three cases were endoscopically managed. Carreere *et al*[21] treated one patient with biliopancreatic fistula with transpapillary pancreatic stenting for 5 mo.

Boulanger *et al*[22] reported a case of PPs with fistula to the common bile duct demonstrated at ERCP and endoscopically managed with biliary stent and, simultaneously, with a second stent placed *via* a transpapillary route across the fistula with one end into the pseudocyst and the other end into the duodenum. Authors don't mention for how long both stents were leaved in place. Al Ali *et al*[23] performed the same endoscopic procedure. In this case, a double pigtail stent placed *via* the transpapillary route across the fistula into

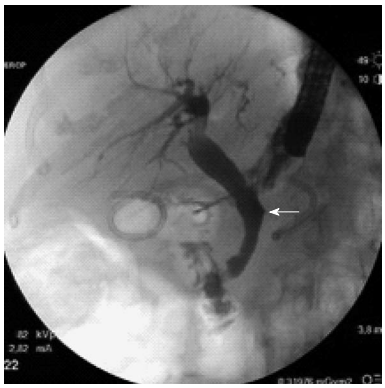

Figure 4 At endoscopic retrograde cholangiopancreatography performed 3 mo later, complete healing of the fistula was documented (arrow).

the PPs was leaved in place for 2 mo.

In our case, we successfully endoscopically managed large PPs with a fistulous communication to the CBD and within necrotic debris, by positioning a plastic biliary stent in association with simultaneous EUS-guided transgastric pancreatic collection drainage with two double pigtail stents and a nasocystic drain.

We believe that this endoscopic approach, especially in cases of very large and infected collection with necrotic debris, should be preferred to the previously described in literature for the better evaluation and the more effective drainage of the cystic cavity. Another advantage of this combined approach is that EUS provides a detailed view of the pseudocyst, the surrounding vascular structures, the anatomy of the region and can determine the content of the PFCs, such as whether it is a simple collection or if significant necrotic debris is present, which would then require a more aggressive endoscopic approach[24]. During the EUS-guided procedure is also possible to aspirate the collection content for biochemical and bacteriological analysis. For these and other reasons, EUS-guided drainage has become the standard procedure for treating symptomatic pancreatic fluid collections[25] and the expertise on this technique is widespread. The simultaneous biliary and pancreatic collection drainage determine, at the same time, a pressure reduction in the bile system and in the pancreatic collection facilitating the healing of the fistula.

In conclusion, this is the first case reported in literature of this rare condition treated with two simultaneous endoscopic procedures, both well coded and safe for the patient, resulted in a rapid healing.

COMMENTS

Case characteristics

A 67-year-old Caucasian woman with history of gallstones and severe acute pancreatitis was admitted to hospital for jaundice, fever and abdominal pain two wk after pancreatitis resolution.

Differential diagnosis

Cholangitis, pancreatitis.

Laboratory tests

WBC 20700 and increased indices of cholestasis.

Imaging diagnosis

Computed tomography scan showed in the region of the pancreatic head an 8 cm x 3 cm pancreatic pseudocyst in communication with the common bile duct (CBD) that was dilated (12 mm) such as the intrahepatic bile ducts; endoscopic retrograde cholangiopancreatography (ERCP) revealed a long, distal biliary extrinsic compression and confirmed a fistulous communication of the middle tract of the CBD with a large pancreatic pseudocyst in the head of the pancreas.

Treatment

Biliary sphincterotomy was performed and a 10 Fr x 7 cm plastic stent was placed in the common bile duct to allow the closure of the fistula. The pseudocyst was drained by endoscopic ultrasound (EUS) and two double pigtail stents were placed between the wall of the stomach and that of pseudocysts for complete drainage.

Experiences and lessons

This case describes a new endoscopic treatment obtained by combination of EUS-guided drainage of the pseudocyst and simultaneous biliary stenting. The advantages of such approach consist in a better evaluation and a more effective drainage of the cystic cavity with the possibility to collect samples for biochemical and bacteriological analysis. Furthermore biliary stenting determines pressure reduction in the bile system and in the pancreatic collection facilitating the healing of the fistula.

Peer review

The authors reported a case of pancreatic pseudocyst with fistula connection with the bile duct that was successfully treated with ERCP stenting and EUS drainage.

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CASE REPORT

Life threatening bleeding from duodenal ulcer after Roux-en-Y gastric bypass: Case report and review of the literature

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Abstract

Acute upper gastrointestinal bleeding is a rare, but serious complication of gastric bypass surgery. The inaccessibility of the excluded stomach restrains postoperative examination and treatment of the gastric remnant and duodenum, and represents a major challenge, especially in the emergency setting. A 59-year-old patient with previous history of peptic ulcer disease had an upper gastrointestinal bleeding from a duodenal ulcer two years after having a gastric bypass procedure for morbid obesity. After negative upper endoscopy finding, he was urgently evaluated for gastrointestinal bleeding. At emergency laparotomy, the bleeding duodenal ulcer was identified by intraoperative endoscopy through gastrotomy. The patient recovered well after surgical hemostasis, excision of the duodenal ulcer and completion of the remnant gastrectomy. Every general practitioner, gastroenterologist and general surgeon should be aware of growing incidence of bariatric operations and coherently possible complications after such procedures, which modify patient's anatomy and physiology.

Key words: Roux-en-Y gastric bypass; Duodenal ulcer; Bleeding; Endoscopy; Emergency surgery

Core tip: Bleeding duodenal ulcer after Roux-en-Y gastric bypass for morbid obesity is a rare, but life threatening situation. Anatomic rearrangement after bariatric operation prevents upper endoscopy from displaying stomach remnant, duodenum, and proximal jejunum. The bleeding duodenal ulcer was identified at emergency laparotomy by intraoperative endoscopy through gastrotomy. After surgical hemostasis, duodenal ulcer excision and completion of the remnant gastrectomy the postoperative course was uneventful.

Ivanecz A, Sremec M, Ćeranić D, Potrč S, Skok P. Life threatening bleeding from duodenal ulcer after Roux-en-Y gastric bypass: Case report and review of the literature. *World J Gastrointest Endosc* 2014; 6(12): 625-629 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i12/625.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i12.625

INTRODUCTION

Obesity in general is described as a global epidemic problem with growing prevalence by World Health Organization[1]. Bariatric surgery has been identified as a safe and effective treatment possibility for morbid obesity and allied comorbidities[2]. Increasing number of bariatric procedures correspond with severity of postsurgical complications[3].

Roux-en-Y gastric bypass (RYGB) is a frequent

surgical procedure for these patients[2]. A significant flaw of RYGB is interrupted access to the bypassed stomach remnant by conventional endoscopy or contrast radiography[4,5]. Interrupted access could be a problem for evaluation and treatment of pathology in the bypassed gastric remnant. Severe complications in area of gastric remnant have been already reported, although the incidence of these complications following RYGB is very low[5-7]. There are retrospective series with 3000 cases of open RYGB presented, 8 patients (0.3%) had bleeding from peptic ulcer disease in the bypassed remnant and intestine[8,9]. Hemorrhage after RYGB could be early or late and in the literature is mostly limited to case reports only[10-12]. Although upper gastrointestinal bleeding originating from ulceration is infrequently reported, it could be a fatal complication.

This report describes the case of a 59-year-old patient, presented in an emergency setting with a life threatening bleeding from duodenal ulcer two years after RYGB.

CASE REPORT

A 59-year-old man presented to the emergency department complaining of weakness, faint and melena. His symptoms started one week before, with passing of darker stool. On the day he was admitted, he visited the market-place, where he fainted. On admission, the patient was pale, normotensive (126/76 mmHg), normocardic (89 per minute) and normopneic (16 per minute) with 85% SpO2. Anal exam showed melena.

His medical history included peptic ulcer disease, psoriatic arthritis and laparoscopic cholecistectomy. The patient has been overweight (BMI 50 kg/m^2) in the past and underwent successful bariatric procedure two years prior at another institution. At the time of admission, there have been no data on exact type of bariatric surgery performed. The patient was a nonsmoker and denied alcohol abuse. The patient was on nonsteroidal anti-inflammatory medication (NSAID). Every day medications included diclofenac (100 mg) two times a day and combination of tramadol with paracetamol (37.5/325 mg) two times a day and once a week 12 mg of metotrexat. At the time of emergency admission, the patient had no prescription for any antiulcer drugs.

Laboratory results revealed decreased level of hemoglobin (83 g/L) and hematocrit (0.24) and coagulopathy. Despite multiple blood transfusions - 4 units of packed red blood cells administered - the patient's anemia persisted. Two hours after admission an emergency upper endoscopy exposed a typical gastrojejunal anastomosis and was advanced 30 cm beyond, without evidence of active bleeding or clot. A longer pediatric endoscope was introduced. During endoscopy patient fainted again and felt stronger abdominal pain. The patient continued to maintain normal blood pressure and pulse. He was transferred to intensive care unit (ICU). A computed tomography (CT) scan demonstrated marked distention of a fluid-filled gastric remnant, a wider duodenal wall, and multiple fluid levels through proximal small intestine (Figure 1). No source of active bleeding was revealed.

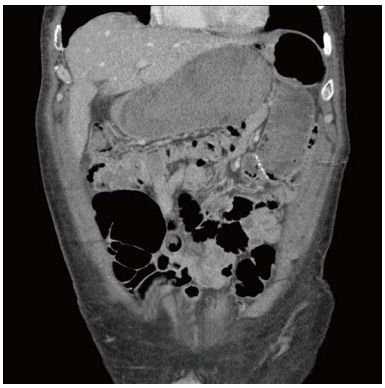

Figure 1 Computed tomography scan showed a fluid-filled gastric remnant, a wider duodenal wall, and multiple fluid levels through proximal small intestine.

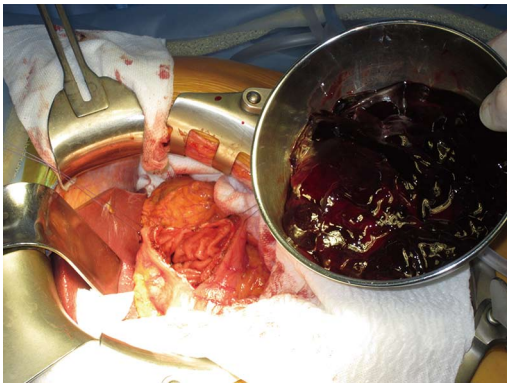

Figure 2 Blood evacuated from gastric remnant.

As a result of ongoing hemorrhage, six hours after admission the patient was taken immediately to the operating room. An emergency midline laparotomy was undertaken.

At surgical exploration a distended gastric remnant, filled with blood was revealed (Figure 2). The duodenum and the proximal jejunal loops were also filled with blood. Through gastrotomy the clothed blood was evacuated and the gastric remnant explored. No active bleeding was identified. Gastrotomy was extended distally to the pyloric region. There were no signs of bleeding; only bile was seen at this part. The duodenal region was covered by visceral adhesions after previous cholecistectomy; no external signs of ulceration could be identified. An intraoperative endoscopy performed trough gastrotomy showed a large ulcer in the posterior part of the second portion of the duodenum with a bleeding branch of gastro-duodenal artery at the bottom (Figure 3). Endoscopic hemostasis with adrenaline injection was ineffective. A gastrotomy was extended once again to duodenotomy and the bleeding ulcer was over-sewn with stitches. Additionally the gastroduodenal artery

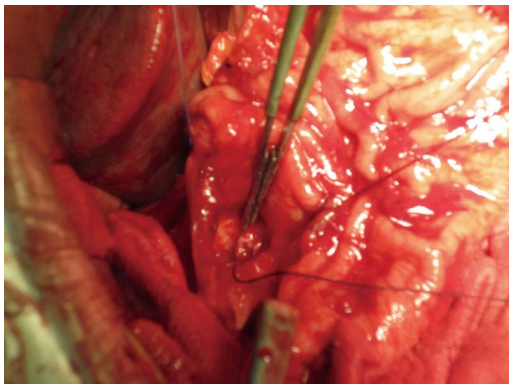

Figure 3 Thirty millimeters wide ulcer on the posterior part of the second portion of the duodenum with a bleeding branch of gastro-duodenal artery marked with tweezers.

was ligated. The ulcer was excised together with first part of the duodenum and the stomach was mobilized to complete the remnant gastrectomy. The duodenal stump was closed primarily in two layered suture line with second layer fixing the stump to the head of the pancreas.

The first postoperative day was characterized by secretion of 1500 mL sero-hemorrhagic fluid trough drains. After initial improvement, decreasing hemoglobin levels were detected again. A relaparotomy was indicated, which revealed a 1 L of clothed blood in the upper abdominal cavity. No source of active bleeding was identified. The blood was evacuated, and the laparotomy closed.

The further postoperative course was uneventful and on 11th post-operative day the patient was discharged. After three months the patient was in very good shape with normal values of hemoglobin.

Histopathology revealed no *Helicobacter pylori* infection in duodenal or gastric tissue. Ulcer was 30 millimeters wide without any neoplastic or dysplastic cells.

DISCUSSION

Acute bleeding duodenal ulcer after Roux-en-Y gastric bypass for morbid obesity is a rare, but life threatening situation[10-12]. The presented patient developed first episode of such complication two years after bariatric operation at another institution. The type of previous surgical procedure (RYGB) was identified only after upper endoscopy and CT scan. The etiology of bleeding was unclear and continued despite aggressive volume replacement and multiple blood transfusions. Urgent laparotomy was the safest option in this life threatening situation. The patient had undergone intraoperative gastrotomy and intraoperative endoscopy through the gastrostomy. An active bleeding from duodenal ulcer was found and managed surgically. Additionally a remnant gastrectomy was performed.

There are many important issues, which should be emphasized in this case. Firstly, bariatric operations are frequently performed in Europe and United States[2]. With increasing number of such procedures, physicians should be familiar with its possible complications. In the emergency setting, the possible pitfall is not to known which type of bariatric surgery patient have had in the past. As in the reported case, the anatomical landmarks of RYGB were revealed only after endoscopic and CT investigations, while in the meantime dealing with threatening hemorrhagic shock.

Another point of interest is the rarity of this late complication. Bleeding from marginal ulcers localized near the pouch-enteric anastomosis is not uncommon after RYGB and could be easily diagnosed and managed by conventional endoscopy[2,13-16]. Bleeding duodenal ulcer after RYGB is rarely reported and it is mostly limited to case reports only[3,13,17-19].

Another issue of this report is difficulty of the diagnostic workup. Evaluation of the bypassed gastric remanant in patients with the possibility of bleeding peptic ulcer disease could be a major challenge. Endoscopic access becomes very difficult after RYGB because of excluded part of the stomach, duodenum, proximal jejunum, and biliary tree[9,20]. Conventional endoscopy of the gastric remnant and duodenum is not possible any more[2]. The long 90-150 cm Roux limb disables endoscopic approach, even with specialized instruments[3,9]. Many different methods have been suggested for displaying the bypassed gastrointestinal tract. These include endoscopy *via* percutaneous gastrostomy access, retrograde endoscopy and virtual gastroscopy using CT scan[21]. In our experience, it has been impossible to visualize the duodenum - even with longer pediatric endoscopes. A minimally invasive technique to access the bypassed stomach after RYGB for endoscopic diagnosis and treatment is described in the literature[9]. Ceppa *et al*[9] proposed a laparoscopic transgastric endoscopy. Such an approach was unattractive in this patient, where highly emergent ongoing bleeding from duodenal ulcer was present.

A special point of interest of this case concerns the proton-pump inhibitors regimens after RYGB. There are non-clear directives for managing patients after RYGB in this regard; however some surgeons advise lifelong proton-pump inhibitors for all patients undergoing RYGB surgery[22]. This patient underwent a complete diagnostic workup before bariatric surgery including upper endoscopy, and duodenal ulcer was diagnosed appropriately. Moreover, the patient was on every day therapy with NSAID for psoriatic arthritis. After the successful RYGB surgery, proton-pump inhibitors were prescribed for several months. Later, proton-pump inhibitors were abandoned. The reason for this is unclear.

Finally, the variety of the surgical management represents another point of interest. When the general and/or the hemodynamic status of the patient are critical, the surgical management should be limited only to a hemorrhage control[16]. After prompt control of the hemorrhage the surgical management was extended

to resection of the gastric remnant. The rationale for this decision was to prevent the development of further possible complications, which include re-bleeding, perforation and gastric malignancy.

In conclusion, due to growing incidence of bariatric operations and possible complications, all healthcare professionals involved in the diagnostic workup of these patients, should be familiar with such procedures which modify patient's anatomy and physiology. They should also be aware of the limitations of imaging methods, including urgent endoscopy.

ACKNOWLEDGMENTS

Written informed consent for this case report was derived from the patient for the purpose of publication. A copy of the document could be presented for review by the Editor-in-Chief of this journal.

COMMENTS

Case characteristics

An 59-year-old male after gastric bypass procedure for morbid obesity with gastrointestinal bleeding.

Clinical diagnosis

The patient presented to the emergency department complaining of weakness, fainting, and melena.

Differential diagnosis

Unexplained hemorrhagic shock with severe abdominal pain.

Laboratory diagnosis

WBC 11.40 k/uL; HGB 8.30 gm/dL; coagulopathy with decreased levels of prothrombine; other liver function test were within normal limits.

Imaging diagnosis

CT scan showed marked distention of a fluid-filled gastric remnant and multiple fluid levels through proximal small intestine. Intraoperative endoscopy confirmed bleeding duodenal ulcer.

Pathological diagnosis

The excised duodenal ulcer was 30 millimeters wide and without any neoplastic or dysplastic cells.

Treatment

At emergency laparotomy, the bleeding duodenal ulcer was identified by intraoperative endoscopy through gastrotomy. Surgical hemostasis, excision of the duodenal ulcer and completion of the remnant gastrectomy was performed.

Related reports

Bariatric surgery modify patient's anatomy and physiology. The treating physicians should be aware of the limitations of imaging methods, including urgent endoscopy.

Term explanation

Roux-en-Y gastric bypass is a common surgical procedure for morbid obese patients.

Experiences and lessons

The increasing number of bariatric procedures correspond with the severity of postsurgical complications.

Peer review

Nice case presentation: succint, linguistically correct, the references are well chosen and conform requirements of the Journal.

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CASE REPORT

Endoscopic therapy for esophageal hematoma with blue rubber bleb nevus syndrome

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Abstract

A 57-year-old woman previously diagnosed with blue rubber bleb nevus syndrome (BRBNS) reported hematemesis. BRBNS is a rare vascular anomaly syndrome consisting of multifocal hemangiomas of the skin and gastrointestinal (GI) tract but her GI tract had never been examined. An upper gastrointestinal endoscopy revealed a large bleeding esophageal hematoma positioned between the thoracic esophagus and the gastric cardia. An endoscopic injection of polidocanol was used to stop the hematoma from bleeding. The hematoma was incised using the injection needle to reduce the pressure within it. Finally, argon plasma coagulation (APC) was applied to the edge of the incision. The esophageal hematoma disappeared seven days later. Two months after the endoscopic therapy, the esophageal ulcer healed and the hemangioma did not relapse. This rare case of a large esophageal hematoma originating from a hemangioma with BRBNS was treated using a combination of endoscopic therapy with polidocanol injection, incision, and APC.

Key words: Blue rubber bleb nevus syndrome; Endoscopic injection sclerotherapy; Incision; Esophageal hematoma; Esophageal hemangioma

Core tip: A patient with a large hemorrhagic esophageal hematoma complicated with blue rubber bleb nevus syndrome was treated using endoscopic injection with polidocanol and incision with an injection needle. The hematoma was then treated with argon plasma coagulation.

Takasumi M, Hikichi T, Takagi T, Sato M, Suzuki R, Watanabe K, Nakamura J, Sugimoto M, Waragai Y, Kikuchi H, Konno N, Watanabe H, Obara K, Ohira H. Endoscopic therapy for esophageal hematoma with blue rubber bleb nevus syndrome. *World J Gastrointest Endosc* 2014; 6(12): 630-634 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i12/630.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i12.630

INTRODUCTION

Blue rubber bleb nevus syndrome (BRBNS) is a rare vascular anomaly syndrome consisting of multifocal

hemangiomas of the skin and gastrointestinal (GI) tract. GI bleeding is a frequent complication that often presents with anemia as a result of chronic occult blood loss. Mortality depends on the GI involvement because it is difficult to treat GI bleeding. The use of endoscopic treatment of GI bleeding for hemangiomas has been reported[1,2]. We treated a single case of a large esophageal hematoma caused by a hemangioma. The treatment involved endoscopic injection, incision of the hematoma using an injection needle, and argon plasma coagulation (APC).

CASE REPORT

A 57-year-old woman was diagnosed with BRBNS because of skin hemangiomas since teen. However, her GI tract had never been examined. The patient had no anemia that suggested occult GI bleeding. She had no other history and did not take any drugs, including anti-thrombotics. In July 2011, she was admitted to a previously attended hospital complaining of hematemesis. An upper GI endoscopy showed a bleeding esophageal hematoma from the thoracic esophagus to the gastric cardia. We treated with total parenteral nutrition and nothing by mouth before endoscopic treatment, however, her anemia progressed. She was referred to our hospital because her hematoma had suspected esophageal or gastric varices.

A physical examination at admission revealed a scar on her left breast from hemangioma resection and multiple bluish hemangiomas on her left arm (Figure 1). She had a height of 154 cm and a weight of 60 kg. The patient's vital signs were stable: blood pressure 120/72 mmHg, heart rate 92 beats per minute, body temperature 36.3 ℃, and SpO2 100% (room air). Laboratory data showed anemia, with a hemoglobin level of 7.4 g/dL. However, a mean corpuscular volume 95.6 fl suggested no chronic bleeding. The patient's white blood cell count, liver function, renal function, and electrolyte balance were normal. The blood urea nitrogen/creatinine ratio was normal. The D dimer level was high (101.7 μg/mL) because of hypercoagulation in multiple hemangiomas. Dynamic computed tomography (CT) revealed an esophageal hematoma but no marked hemoperfusion to the hematoma (Figure 2). Upper GI endoscopy showed a growing esophageal hematoma with oozing bleeding (Figure 3A and B). The hematoma was large and bulging, and it was difficult to pass the endoscope over the hematoma. We inferred that this hematoma originated from hemangiomas related to BRBNS and that the hematoma had slow inflow from vessels such as esophageal varices because it had grown since it was identified at the other hospital. The patient had no history of vomiting, abdominal straining after excessive eating and drinking.

We first used endoscopic injection with polidocanol (aethoxysclerol; ASKA Pharmaceutical Co. Ltd.) as a sclerosant for endoscopic injection sclerotherapy (EIS) for esophageal varices. This agent was used to obstruct the inflow vessels to the hematoma because it was dependent on esophageal varices. Twenty-four ml of 1% polidocanol was injected into the hematoma using a 23 G injection needle (Varixer; TOP Corp., Tokyo, Japan) (Figure 3C). Ten minutes after polidocanol injection, the hematoma was incised using the same injection needle to reduce the pressure within it (Figure 3D). Finally, argon plasma coagulation (APC: APC300; Amco Corp., Tokyo, Japan) was applied to the edge of the incision. We finished the endoscopic procedure because no active bleeding or oozing from the hematoma occurred. The

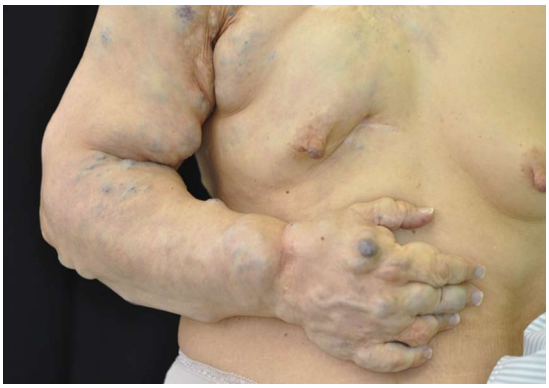

Figure 1 Physical examination at admission. The patient had a scar from the excision of hemangiomas on her right breast and multiple bluish hemangiomas on her right arm.

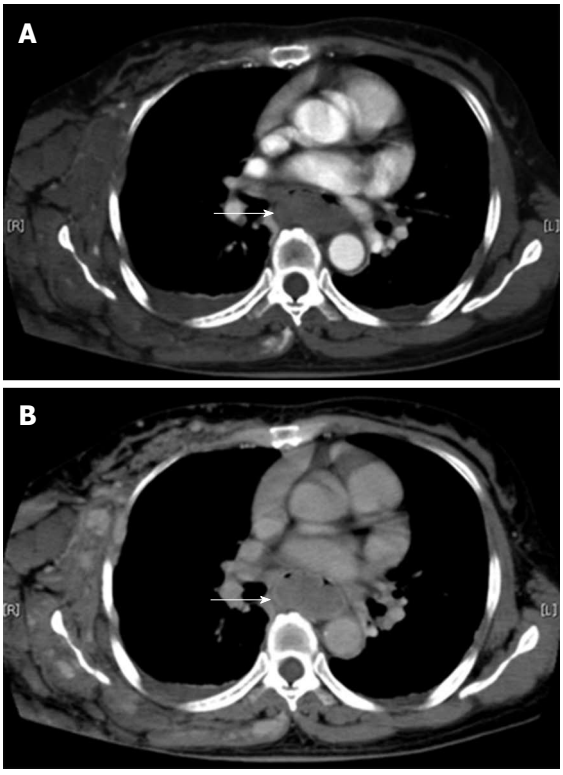

Figure 2 Dynamic computed tomography study. A: Early phase; B: Late phase. An esophageal hematoma was found, but there was no hemoperfusion to the hematoma.

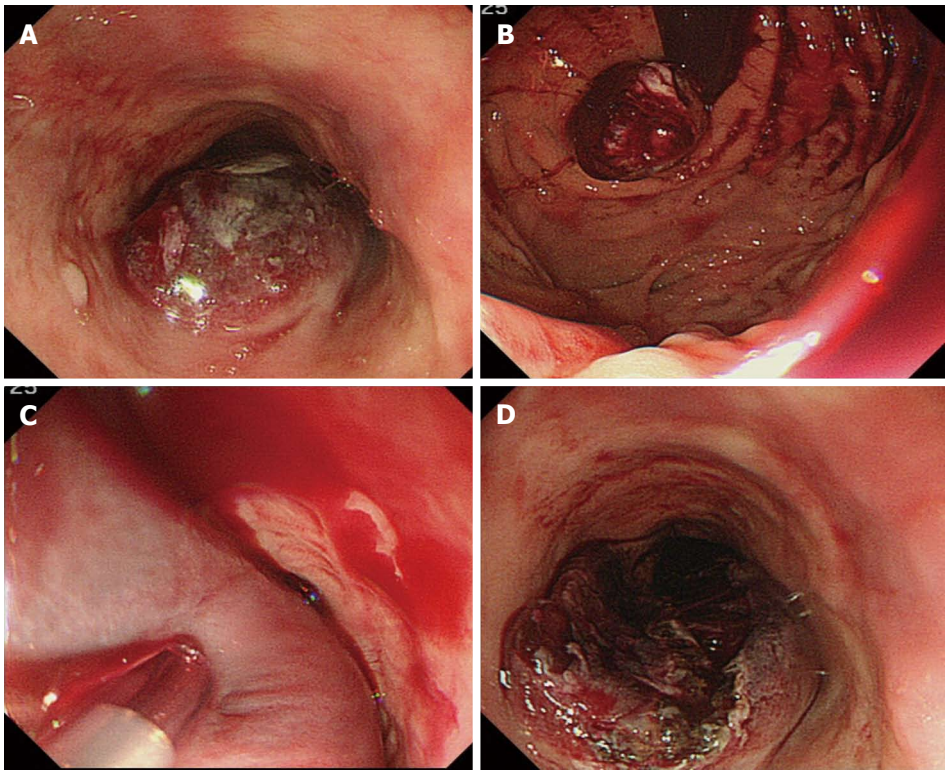

Figure 3 Endoscopic images of the esophageal hematoma taken before and during endoscopic therapy. A and B: Esophageal hematoma from the thoracic esophagus to the gastric cardia with oozing bleeding; C: Endoscopic injection sclerotherapy with polidocanol was applied to the hematoma; D: After injection of polidocanol, the hematoma was incised using an injection needle.

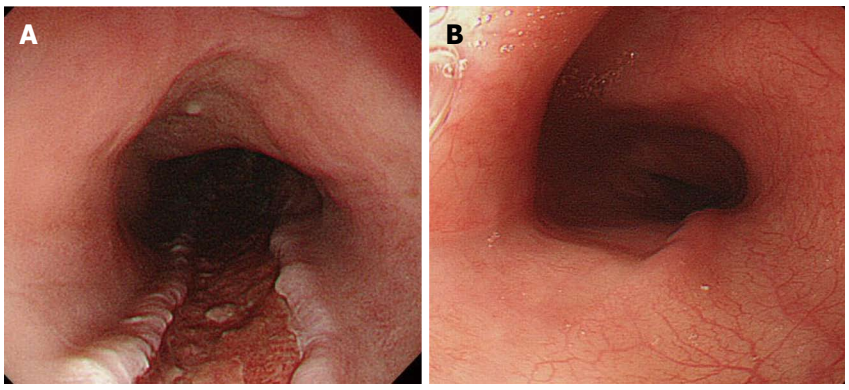

Figure 4 Endoscopic images after endoscopic therapy. A: Seven days after endoscopic therapy, the hematoma had disappeared; B: Two months after endoscopic therapy, the esophageal ulcer healed, and the hematoma had not relapsed.

patient received six units of transfused blood. Seven days after the treatment, upper GI endoscopy showed that the hematoma had disappeared (Figure 4A). The anemia did not progress. A liquid diet was started and was increased gradually to solid food. Ten days after endoscopic therapy, colonoscopy (CS) and capsule endoscopy (CE) were performed to check other hemorrhagic lesions and hemangiomas related to BRBNS in the small intestine and colon. Although CS revealed no hemangiomas, CE revealed a bluish lesion that implied the existence of a hemangioma in the small intestine. Two months after the endoscopic therapy, the esophageal ulcer healed and the hemangioma did not relapse (Figure 4B).

DISCUSSION

BRBNS is a rare disease associated with multiple rubbery cavernous hemangiomas on the skin and GI tract mucosa. Bean[3] first described BRBNS with cutaneous and GI malformations in 1958. The incidence of this syndrome is very low, and only approximately 200 cases have been described in the literature[4]. Histologically, BRBNS hemangiomas correspond to venous malformations. Vascular malformations are similar to hemangiomas and consist of abnormal vascular channels lined with a single layer of dysplastic endothelium. However, these lesions do not regress the way hemangiomas do. Vascular

malformations are present at birth and are congenital[5]. They consist of mature endothelial-lined channels with insufficient surrounding smooth muscle[6]. For convenience, we use the words "hemangioma" to describe both vascular malformations and hemangiomas in this case report. Hemangiomas related to BRBNS have no malignant potential. However, the most important clinical concern is the high probability of fatal GI bleeding or chronic severe anemia[1]. The GI involvement in BRBNS is typically minimal, circumscribed, and multifocal[6]. The most common site of bowel involvement in BRBNS is the small intestine. In the case described in this study, CE revealed suspected hemangiomas. An upper GI endoscopy revealed a large intramural hematoma, but no hemangioma. The exact pathogenesis of the intramural hematoma in the esophagus is unclear. Intramural esophageal hematomas are generally characterized by a hemorrhagic episode that starts within the submucosa of the esophagus. Vomiting and abdominal straining, prior endoscopic procedures, and bleeding disorders are the common predisposing factors[7]. We were unable to prove that the hematoma had originated from a hemangioma due to BRBNS because the patient's GI tract was not examined. However, we inferred that the large hematoma was related to the hemangiomas related to BRBNS because no other trigger such as vomiting or excessive eating or drinking was found.

EIS has been widely used to treat esophageal varices. We first considered that the pathology of the large hematoma was similar to esophageal varices. Intramural hematoma of the esophagus is reportedly a rare complication after EIS[8,9]. An intramural hematoma after EIS is an iatrogenic complication. It is formed by blood inflow because of faulty EIS. The use of an incision to treat the intramural hematoma after EIS was needed to reduce the pressure of the large hematoma and prevent its growth[9]. Although CT did not reveal inflow vessels to the hematoma in this case, we inferred that the hematoma was enlarged by slight and slow inflow from esophageal vessels. We selected endoscopic injection using polidocanol before incision to obstruct the inflow vessels to the hematoma and prevent the risk of bleeding. The hematoma was then incised using the same injection needle after confirmation that there was no bleeding from the pinhole or hematoma growth. Finally, APC was applied to the edge of the incision to stop any oozing bleeding that occurred after the incision. The presence of oozing bleeding after the incision suggested there was slow inflow to the hematoma. Seven days after endoscopic treatment of the hematoma, upper GI endoscopy showed that it had disappeared. The combination treatment consisting of endoscopic therapy, polidocanol injection, incision, and APC was effective.

An intramural hematoma of the esophagus might resolve spontaneously without therapeutic intervention and have a benign course[8]. However, the hematoma in this patient expanded and was growing. Symptom relief was rapid after incision of the hematoma. The patient was able to resume eating sooner than might have been predicted based on prior reports[7-11]. Following conservative therapy, symptoms usually begin to resolve 36-72 h after treatment and disappear completely in 2-3 wk[8]. The start of oral intake was sooner than previous cases[9-11]. It was possible for our patient to resume oral intake three days after the endoscopic incision, although it took approximately one week with conservative therapy in other studies[7,8]. In conclusion, a large esophageal hematoma from a bleeding hemangioma with BRBNS was treated using endoscopic techniques. It is noteworthy that an incision of the hematoma prevented its growth. This method is regarded as applicable not only to hematoma with BRBNS but also to hematomas with other GI diseases.

COMMENTS

Case characteristics

A 57-year-old woman previously diagnosed with blue rubber bleb nevus syndrome (BRBNS) reported hematemesis.

Clinical diagnosis

An upper gastrointestinal endoscopy showed a bleeding esophageal hematoma from the thoracic esophagus to the gastric cardia.

Differential diagnosis

Esophageal varices and intramural hematoma of the esophagus.

Laboratory diagnosis

Laboratory data showed anemia with a hemoglobin level of 7.4 g/dL; however, mean corpuscular volume 95.6 fL suggested no chronic bleeding.

Imaging diagnosis

Dynamic computed tomography revealed an esophageal hematoma but no marked hemoperfusion to the hematoma.

Pathological diagnosis

No histological examination was done in this case.

Treatment

Endoscopic treatment of polidocanol injection was applied, with incision by injection needle and argon plasma coagulation to the hematoma.

Related reports

The incidence of BRBNS is very low. Approximately 200 cases have been described in the literature. Moreover, very few cases of intramural hematoma of the esophagus treated with endoscopy have been reported in the literature. Their treatment is controversial.

Term explanation

It is noteworthy that an incision of the hematoma prevented its growth. This method is regarded as applicable not only to hematoma with BRBNS but also to hematomas with other GI diseases.

Experiences and lessons

This case demonstrates that treatment of esophageal intramural hematoma using endoscopic techniques was more effective than conservative therapy to relieve her symptoms rapidly.

Peer review

The authors have described a case of esophageal hematoma with BRBNS that was treated using endoscopic techniques. The article describes novel treatment applied to an intramural hematoma of the esophagus.

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