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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

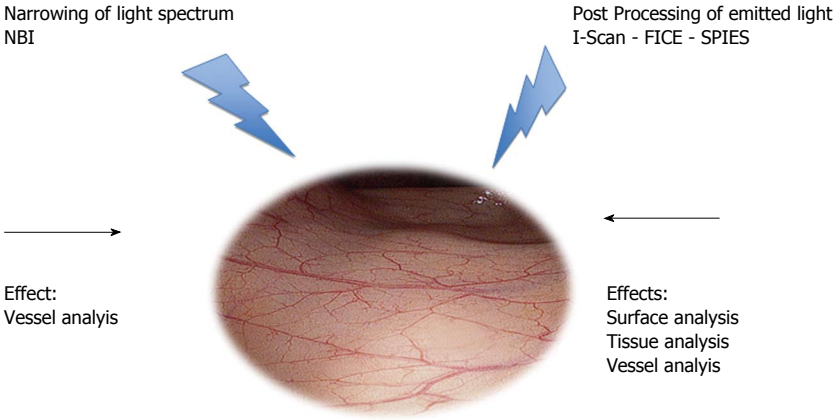

Figure 1 Digital chromoendoscopy. Digital chromoendoscopy can be achieved by simply pressing a button on the endoscope. NBI focuses on vessel architecture by narrowing the light spectrum which is emitted to the mucosa. Fujinon Intelligent Color Enhancement System, *i*-scan and STORZ Professional Image 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-

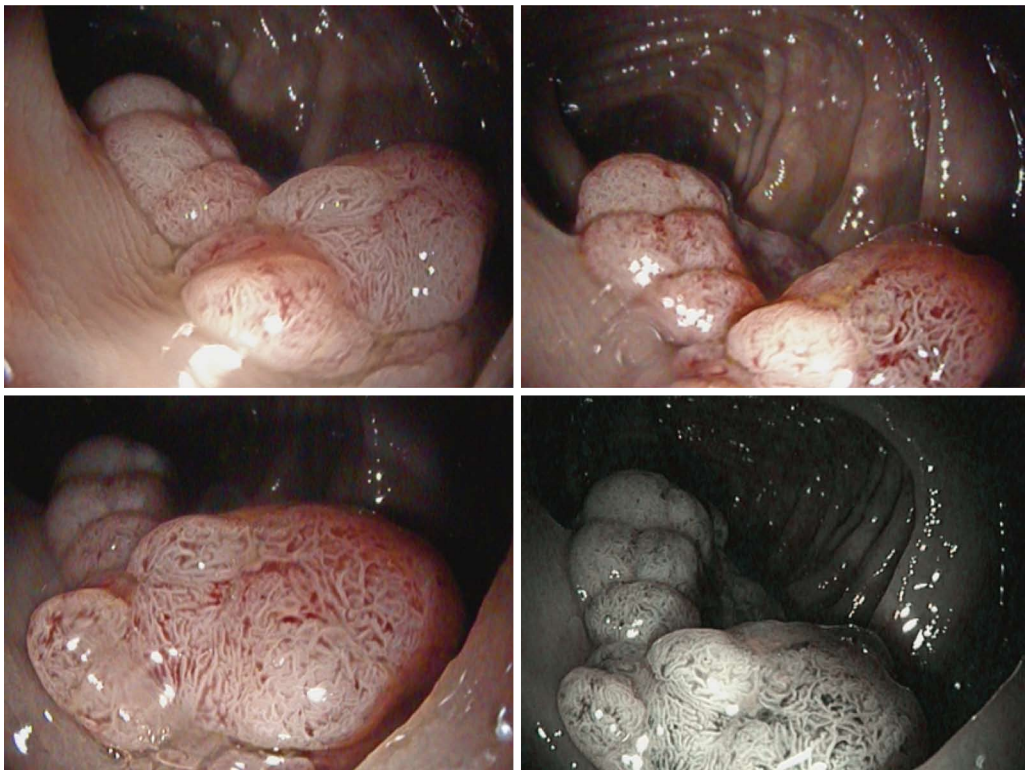

Figure 2 Virtual chromoendoscop using STORZ Professional Image Enhancement System of colorectal lesions.

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-

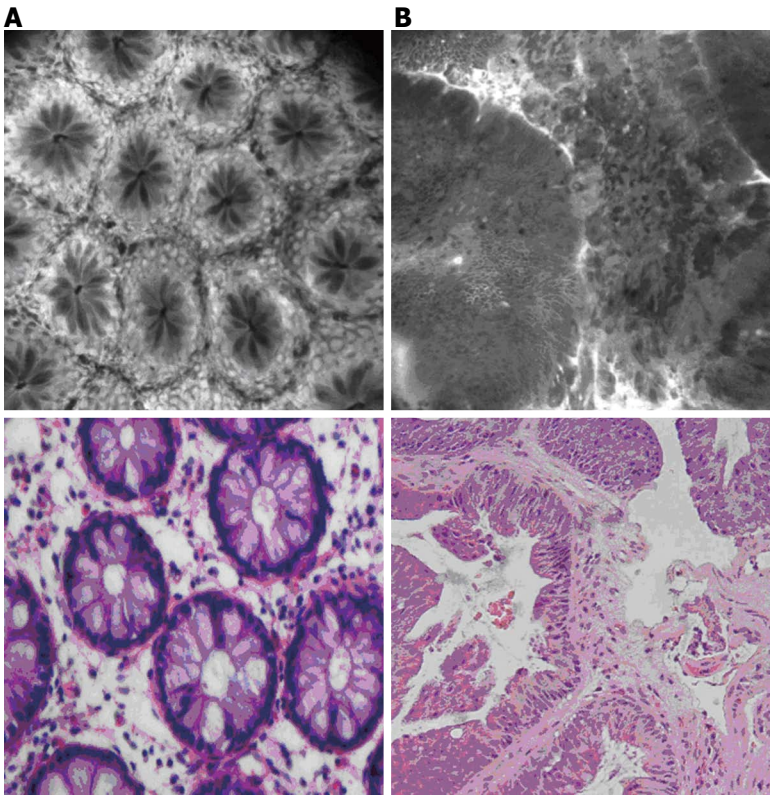

Figure 3 Confocal Endomicroscopy in normal colonic epithelium (A) and of a colonic dyspalsia (B).

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

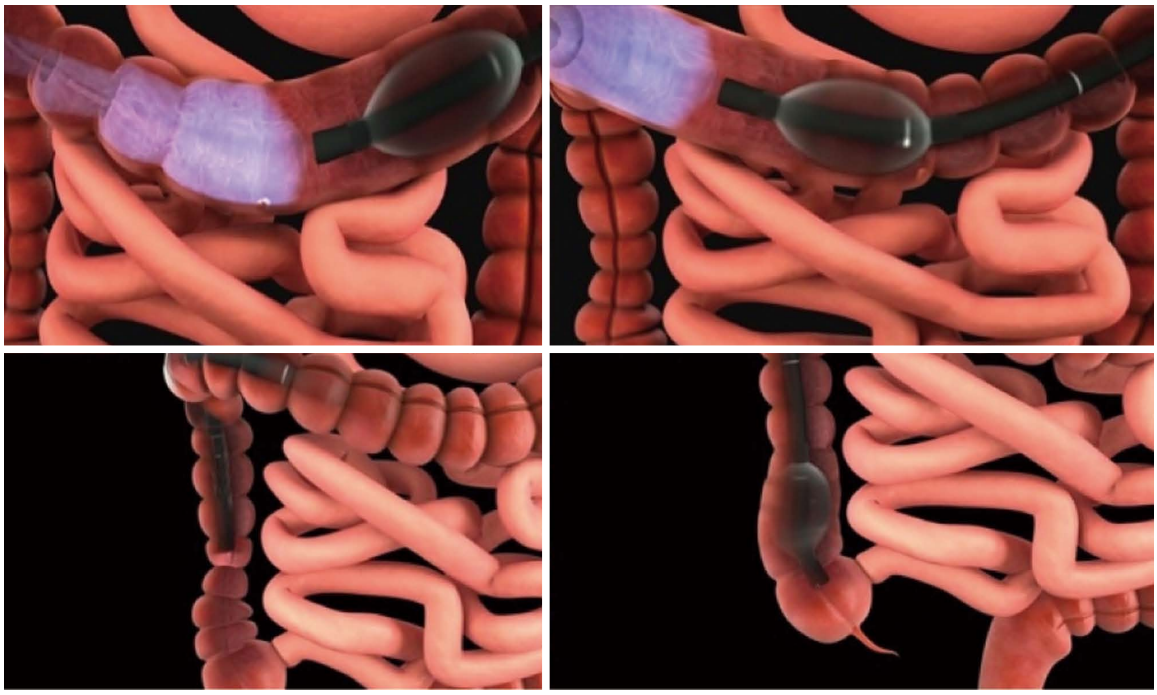

Figure 4 GEye balloon colonoscopy with inflated balloon at the distal tip of the colonscope the balloon is inflated to straight intestinal folds in the colon.

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

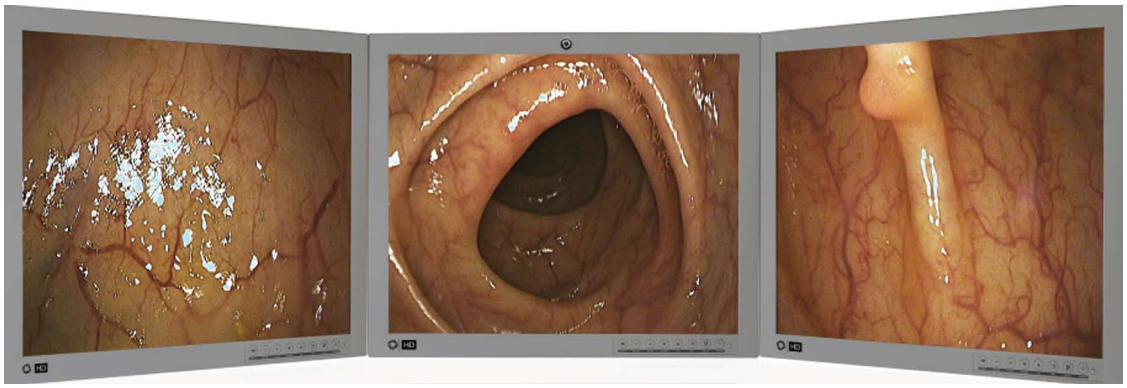

Figure 5 Full spectrum endoscopy colonoscopy utilizes unique imaging technology, which allows the endoscopist to view 330 degrees while maintaining identical standard colonoscope technical features. Property of full spectrum endoscopy, EndoChoice, Alpharetta, GA, United States.

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

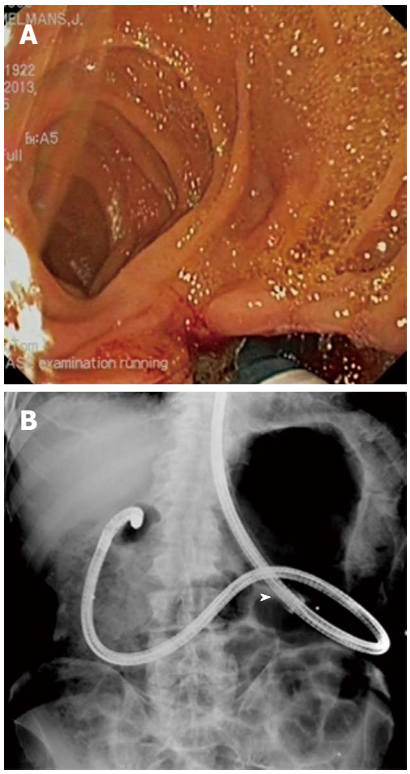

Figure 1 View Billroth Ⅱ. A: Endoscopic view of Billroth Ⅱ gastrojejunostomy with sharp angulation towards the afferent limb while retracting the single-balloon enteroscope. Note the mucosal tear at the short angle of the afferent limb at the end of the endoscopic retrograde cholangiopancreatography 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.

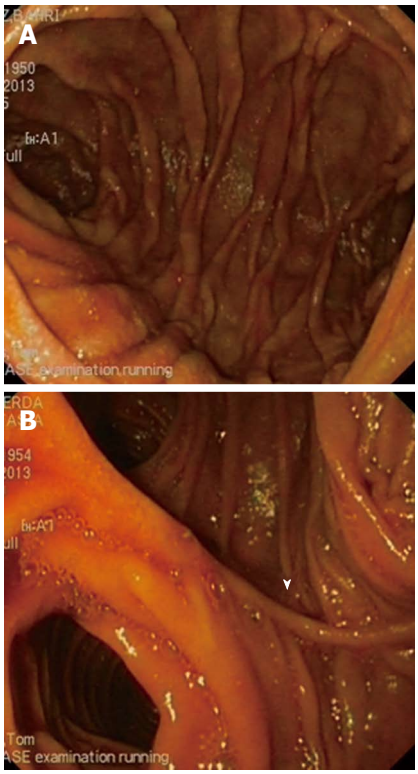

Figure 2 Endoscopic view of Roux-en-Y reconstruction. A: Endoscopic view of an end-to-side Roux-en-Y reconstruction with view on the afferent limb (right) and common limb (left). The white arrow denotes the operative scar of the anastomosis; B: Endoscopic view of a side-to-side Roux-en-Y reconstruction 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

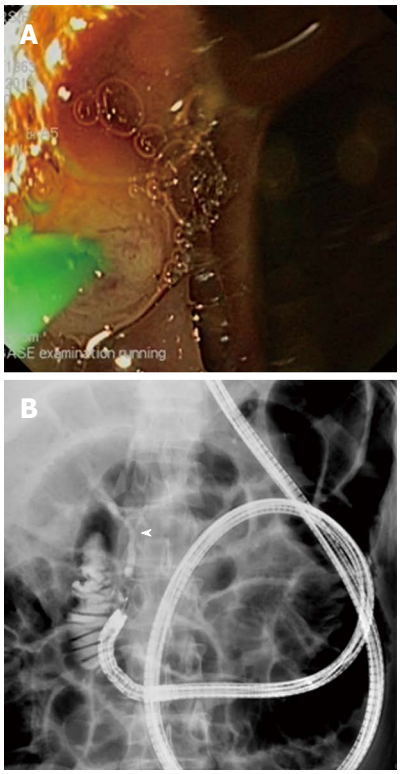

Figure 3 View. A: Endoscopic view of the distal approach to cannulate an intact papilla of Vater using a straight catheter with a forward-viewing endoscope. In order to cannulate in the direction of the common bile duct, the papilla is rotated into the 7 o'clock position; B: Radiological view of the 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.

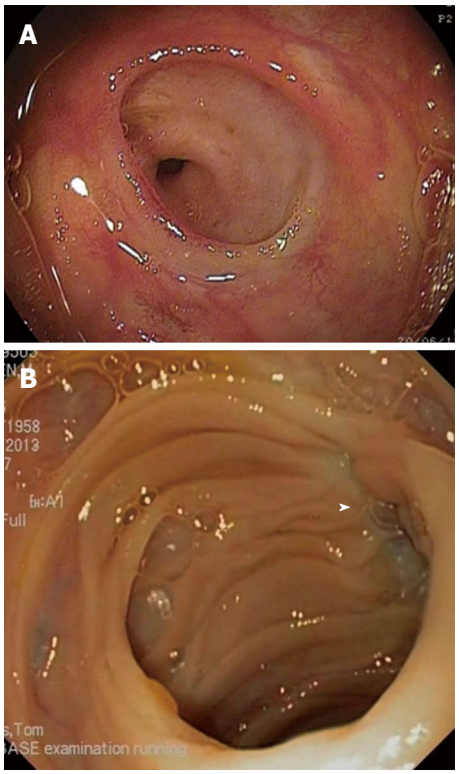

Figure 4 Endoscopic view of bilioenteric anastomosis. A: Endoscopic view of a normal end-to-side bilioenteric anastomosis; B: Endoscopic view of a stenosis at the level of the bilioenteric anastomosis. Only scar tissue (white arrow) indicates the location of the anastomosis without visible opening.

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

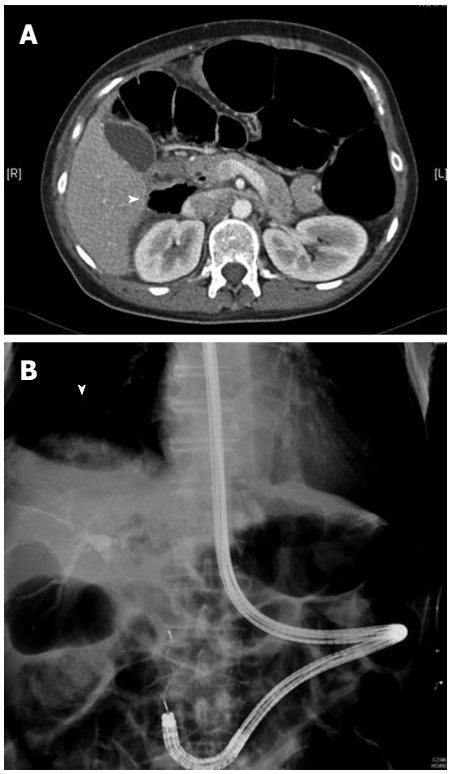

Figure 5 A patient with Roux-en-Y gastric bypass. A: Computed tomography of a retroperitoneal perforation (white arrow) at the level of papilla of Vater after sphincterotomy and sphincteroplasty in a patient with Roux-en-Y gastric bypass; B: Radiological view of hepatic capsule dehiscence without free 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-

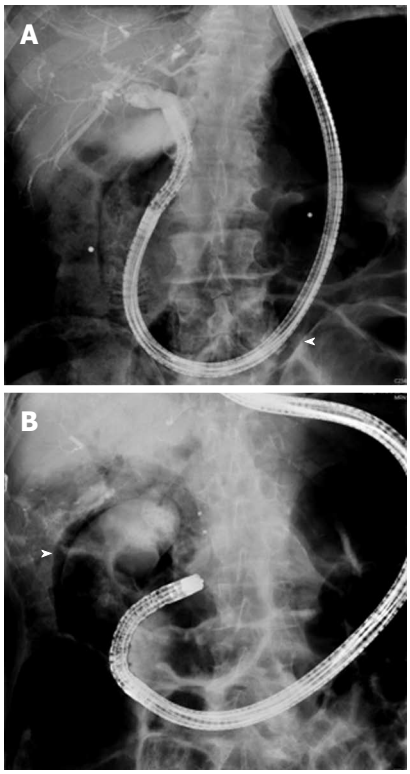

Figure 6 Radiological view. A: Radiological view of direct cholangioscopy with the single-balloon enteroscope inside the common bile duct and with the overtube (white arrow) inside the afferent limb of a Billroth Ⅱ patient; B: Radiological view of free air around the contrast-filled gallbladder (white 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.

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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

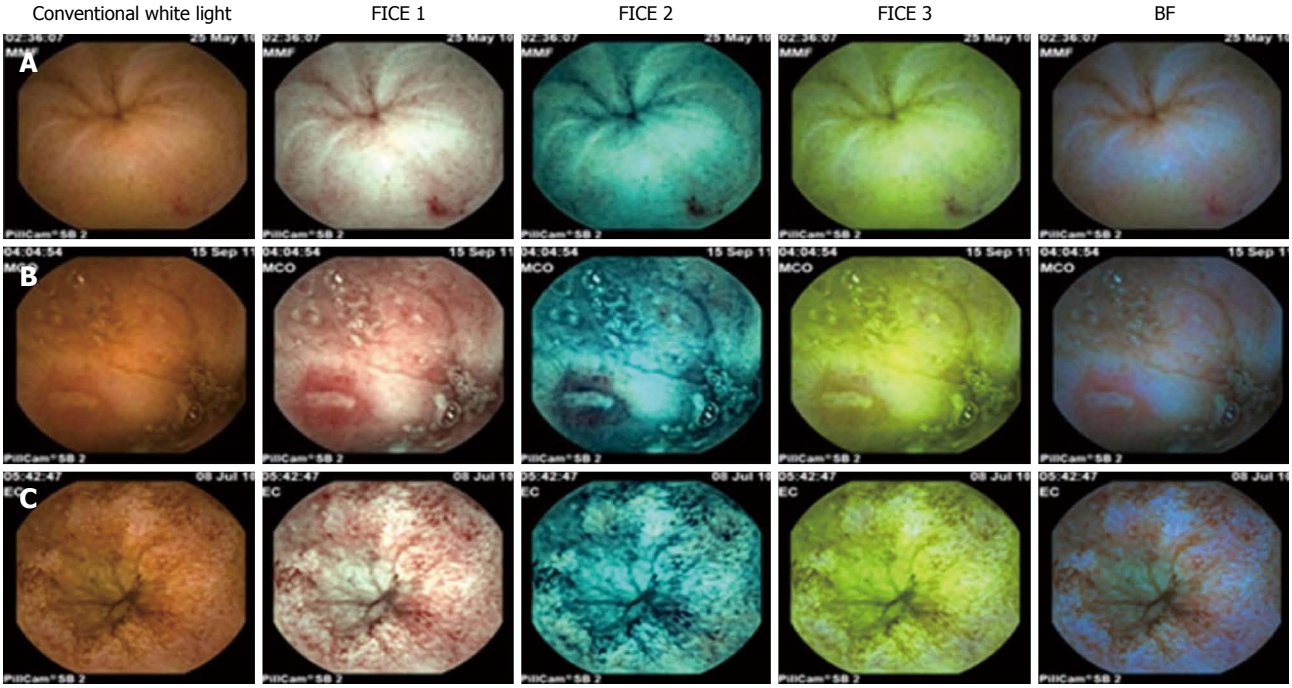

Figure 1 Small bowel mucosal lesions under conventional white light and virtual chromoendoscopy. A: Angioectasia; B: Ulcer; C: Villous edema.

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],

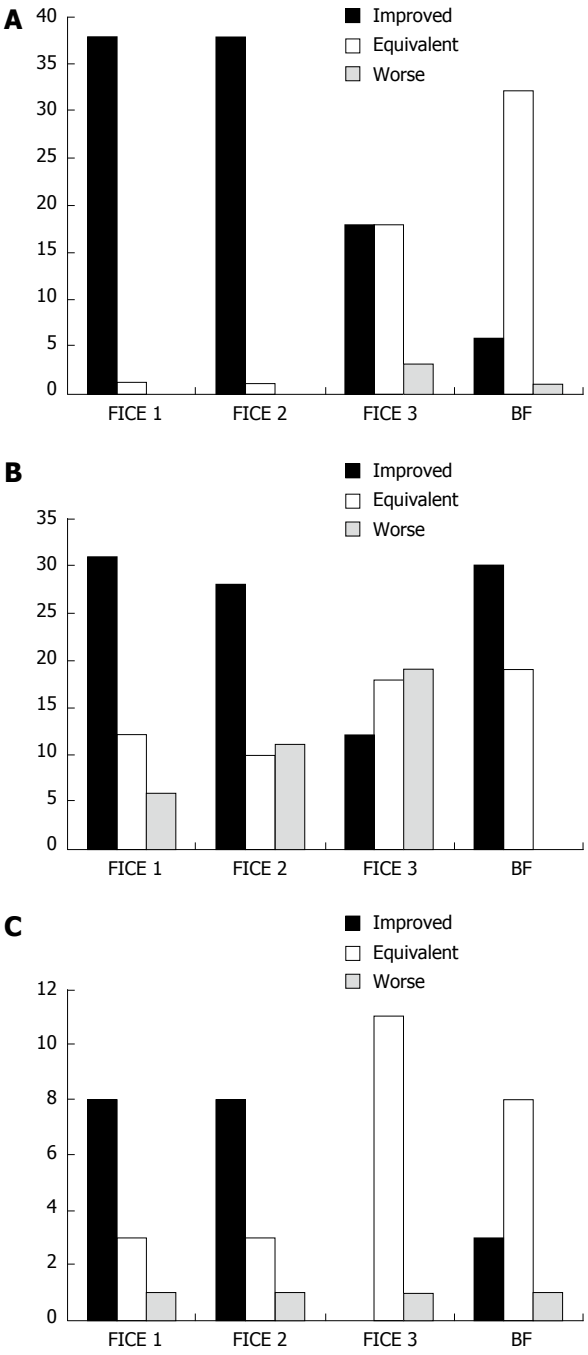

Figure 2 Delineation. A: Of angioectasias with all different settings of virtual chromoendoscopy: comparison with conventional white light; B: Of ulcers or erosions with all different settings of virtual chromoendoscopy: comparison with conventional white light; C: Of villous edema or atrophy with all 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

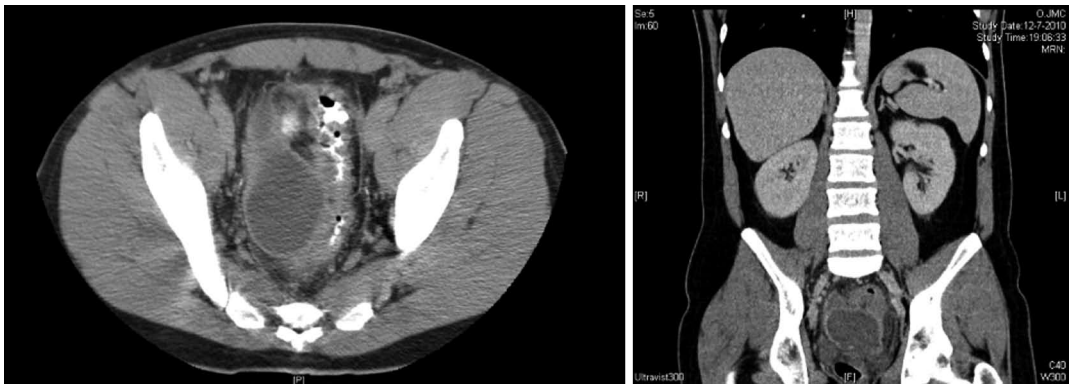

Figure 1 Axial and coronal computed tomography views of pelvic abscess adjacent to thickened sigmoid wall in a patient with acute diverticulitis.

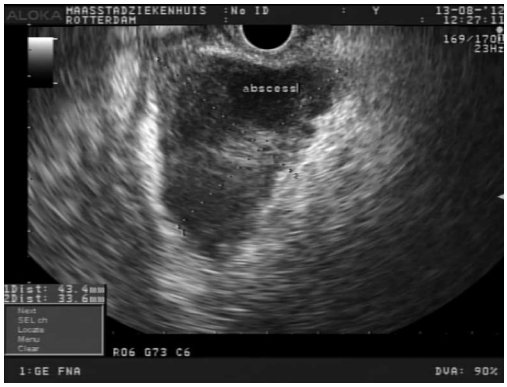

Figure 2 A pelvic abscess (43 mm × 33 mm) visualized with a linear echoendoscope (7.5 MHz).

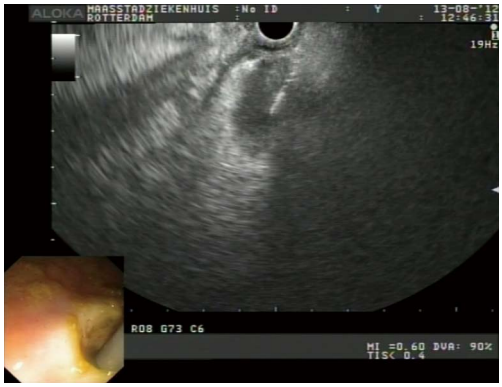

Figure 3 Endoscopic ultrasound (inlet endoscopic) image showing a cystotome used to dilate the tract.

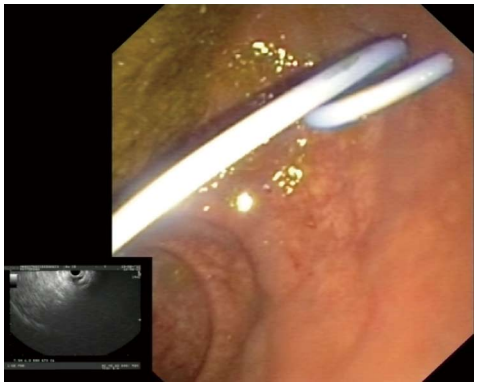

Figure 4 Endoscopic image showing the transrectal placement of 7 *Fr* double pig tail plastic stent.

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

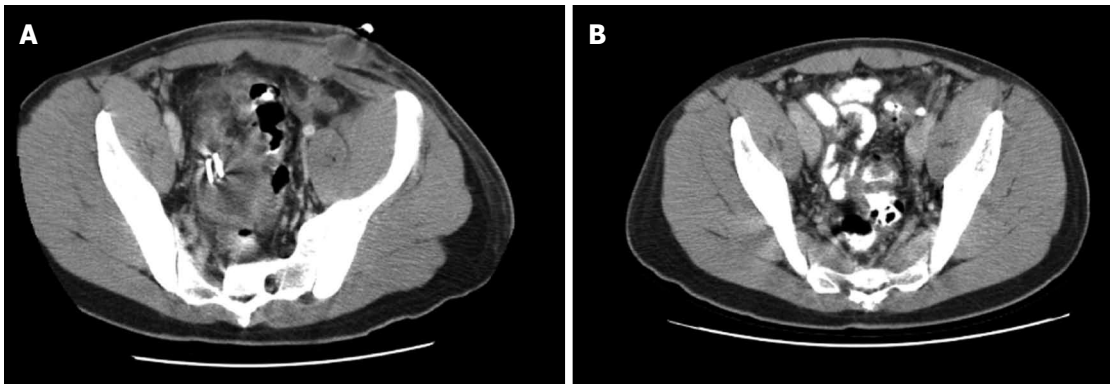

Figure 5 Follow-up computed tomography scans showing initially partial (A) and later complete (B) resolution of pelvic abscess.

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.

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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-

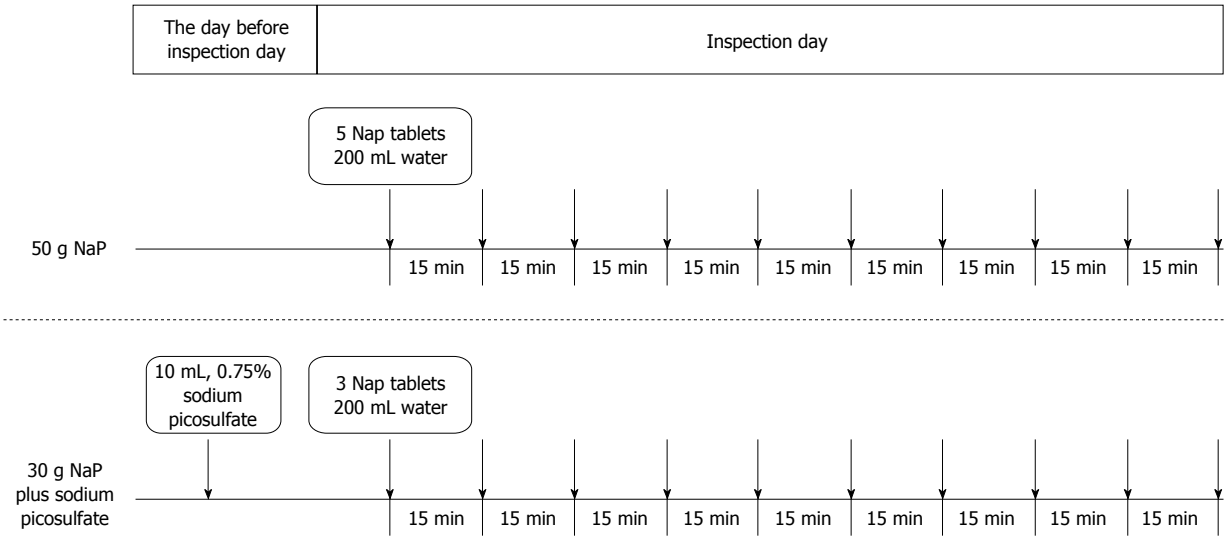

Figure 1 Study protocol for the bowel preparations. Sodium phosphate (NaP) was administered at a rate of five tablets (5 g) or three tablets (3 g) every 15 min with 200 mL of water beginning five to six hours before the colonoscopy. Sodium picosulfate was taken with 200 mL of water on the night before 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).

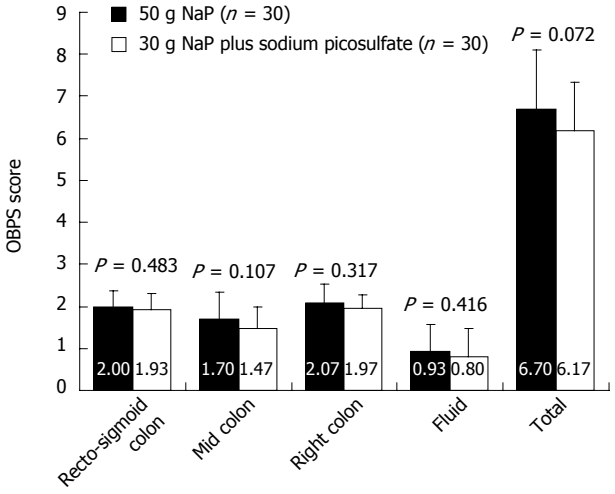

Figure 2 The mean Ottawa bowel preparation scale scores. There was a trend toward a lower mean total score in the 30 g NaP plus sodium picosulfate group compared to the 50 g NaP group, but this difference was not statistically significant (Mann-Whitney's U-test, P = 0.072).

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

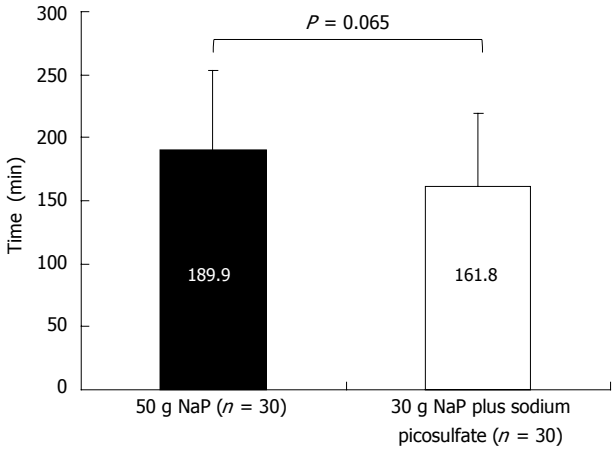

Figure 3 The mean time required for the completion of the bowel preparation. There was a trend toward a shorter bowel preparation time in the 30 g sodium phosphate (NaP) plus sodium picosulfate group compared to the 50 g NaP group, but this difference was not statistically significant (Student's *t*-test, $P = 0.065$).

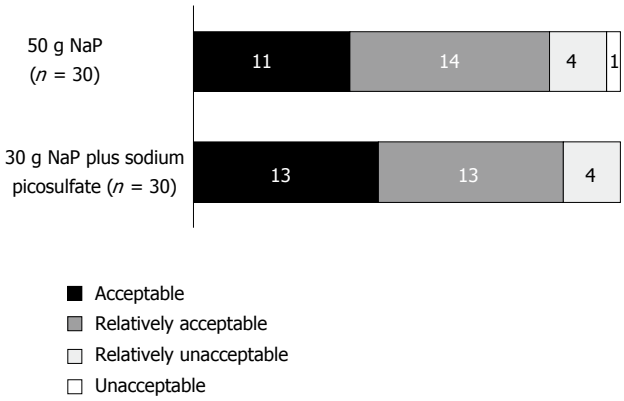

Figure 4 The patients' overall impressions of the bowel preparations as assessed on a four-category Likert scale. There was no significant difference between the two groups in acceptabilities (*i.e.*, the "acceptable" plus "relatively acceptable" scores) of the preparations (Fisher's exact test, $P = 0.500$).

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).

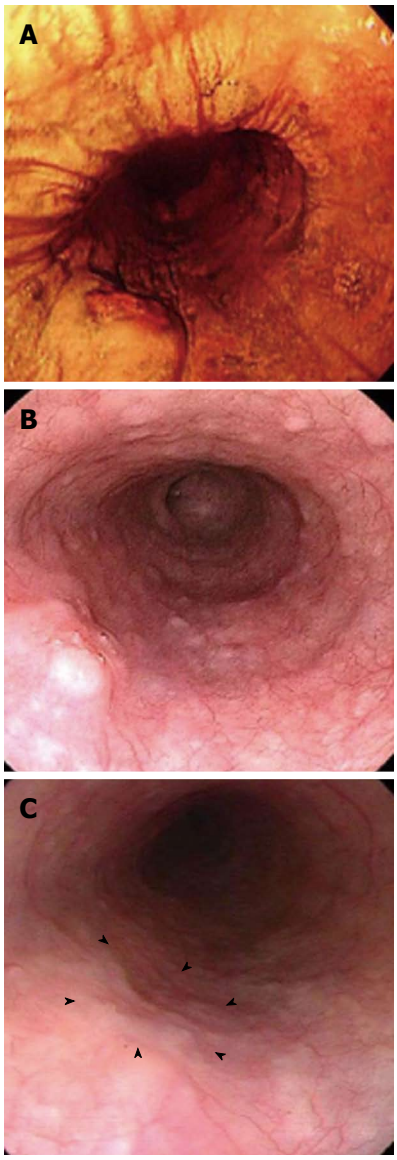

Figure 1 The endoscopic findings. A: The first endoscopy (at the previous clinic) showed a submucosal-like tumor of approximately 10 mm in diameter. The lesion, except for the erosion at the top, was stained with Lugol's solution; B: The second endoscopy (performed two weeks after the first endoscopy) 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

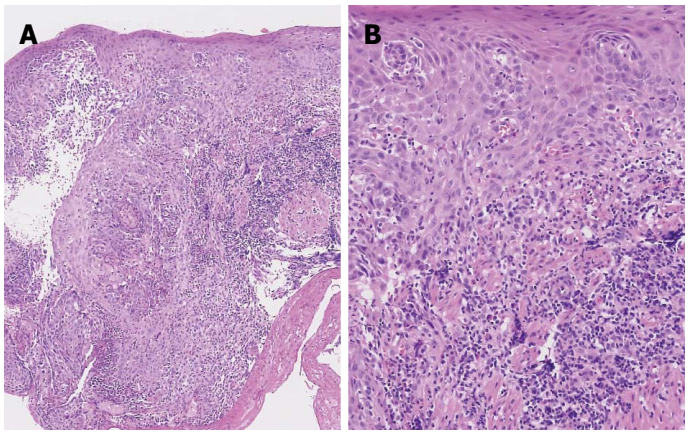

Figure 2 The endoscopically-biopsied material. A: The inflammatory cell infiltration in the mucosa was remarkable (HE staining, original magnification × 40); B: Squamous cell carcinoma with prominent infiltration of lymphoid cells was revealed (HE staining, original magnification × 100).

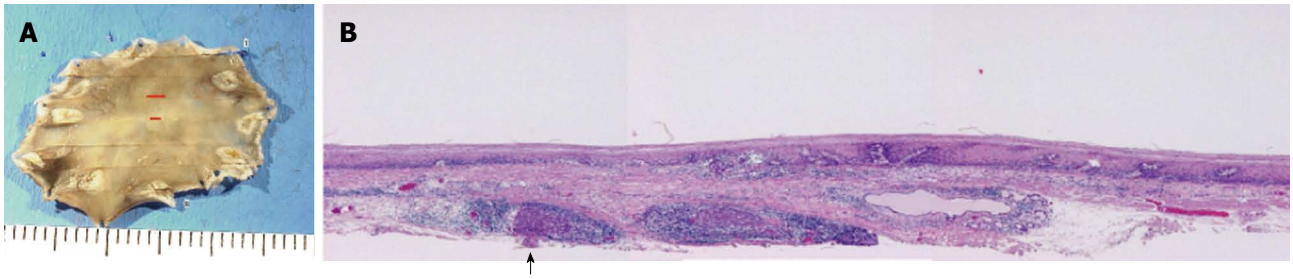

Figure 3 The endoscopically-resected material. A: The gross appearance of the resected esophageal mucosa is shown. There was a superficial smooth tumor measuring 6 mm × 3 mm in the resected mucosa (line), and it was difficult to find the tumor macroscopically; B: The tumor, with prominent lymphoid cell infiltration, was mainly visible in the submucosal layer (HE staining, original magnification × 10). The vertical margin was positive (arrow).

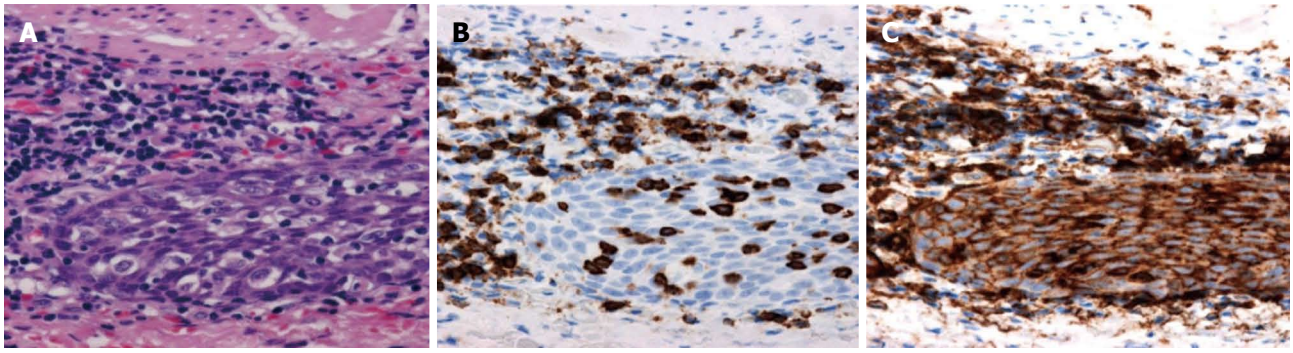

Figure 4 The histopathological findings. A: Poorly differentiated squamous cells and lymphocytes that had infiltrated into the carcinoma cell nests were observed (HE staining, original magnification × 400); B: Prominent infiltration of cytotoxic T lymphoid cells that stained positive for CD8 was observed 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

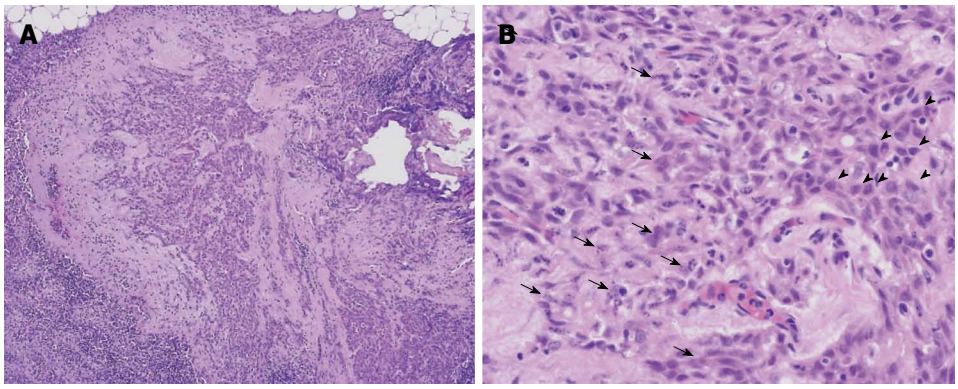

Figure 5 The surgically dissected lymph node from the neck area. A: In the lymph node, which was 5 mm in diameter, a metastasis that was 2 mm in diameter was found (HE staining, original magnification × 40); B: Histological evaluation showed that lymphocytes had infiltrated around the carcinoma cells (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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Acknowledgments

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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