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REVIEW

Safety considerations in laparoscopic surgery: A narrative review

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Abstract

Laparoscopic surgery has many advantages over open surgery. At the same time, it is not without its risks. In this review, we discuss steps that could enhance the safety of laparoscopic surgery. Some of the important safety considerations are ruling out pregnancy in women of the childbearing age group; advanced discussion with the patient regarding unexpected intraoperative situations, and ensuring appropriate equipment is available. Important perioperative safety considerations include thromboprophylaxis; antibiotic prophylaxis; patient allergies; proper positioning of the patient, stack, and monitor(s); patient appropriate pneumoperitoneum; ergonomic port placement; use of lowest possible intra-abdominal pressure; use of additional five-millimetre (mm) ports as needed; safe use of energy devices and laparoscopic staplers; low threshold for a second opinion; backing out if unsafe to proceed; avoiding hand-over in the middle of the procedure; ensuring all planned procedures have been performed; inclusion of laparoscopic retrieval bags and specimens in the operating count; avoiding 10-15 mm ports for placement of drains; appropriate port closures; and use of long-acting local anaesthetic agents for analgesia. Important postoperative considerations include adequate analgesia; early ambulation; careful attention to early warning scores; and appropriate discharge advice.

Key Words: Laparoscopy; Laparoscopic surgery; Minimally invasive surgery; Key-hole surgery; Patient safety; Safe surgery; Safe laparoscopy

Core Tip: Check for pregnancy in women of the childbearing age group. Make an alternative advanced plan with the patient regarding unexpected intra-abdominal

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circumstances. Consider adequate thromboprophylaxis and antibiotic prophylaxis. Intraoperatively, surgeons should ensure correct patient positioning and placement of stack and monitor(s). Establishing pneumoperitoneum safely, proper use of energy devices/staplers, use of lowest possible intra-abdominal pressure, avoidance of 10-15 millimetre ports for placement of drains; and a thorough "time out" at the end are some of the other important intraoperative considerations. The operating count by nurses should include specimens and retrieval bags. Important postoperative considerations include analgesia, early ambulation, and careful attention to early warning scores.

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INTRODUCTION

Laparoscopic surgery could be regarded as one of the greatest advances in the field of surgery. It has brought with it a revolution in the use of digital and robotic technology in surgical practice. It has radically shortened the patient recovery times compared to the 'open' operations. Even more remarkably, these gains have been made whilst simultaneously enhancing the quality of surgery[1,2]. Laparoscopic surgery is associated with less pain, fewer wound infections, reduced hospital stay, reduced morbidity and mortality and early return to work and improved overall quality of life [3,4]. However, when laparoscopy was first introduced there were concerns regarding its safety[5,6]. Fortunately, with time as surgical teams have progressed over their learning curves, many of the initially reported complications have become relatively infrequent[7].

In this article, we review some of the key areas that could enhance the safety of laparoscopic surgery. We have structured this article to simulate a patient's journey into preoperative, perioperative, and postoperative considerations.

PRE-OPERATIVE PLANNING

Patient selection

Patient selection plays a key role in enhancing the safety of laparoscopic surgery[8,9]. In addition to the risks associated with a general anaesthetic, laparoscopy is associated with risks due to increased intra-abdominal pressure (IAP) and in some cases extreme patient positioning[10]. There is no absolute contraindication to laparoscopic surgery but patients with significant medical comorbidities should be treated with caution just like any other surgery. Some patients may be suitable for laparoscopic surgery but not the corresponding open procedure and this should be discussed with the patient in advance. The morbidity and mortality of the open surgery may be too high (such as frail patients or those suffering from severe obesity) and surgeons may need to either back out without performing any procedure (such as when faced with extensive adhesions or a cirrhotic liver or a huge liver) or perform a different procedure to the one planned (such as a subtotal cholecystectomy instead of a total cholecystectomy; or sleeve gastrectomy in place of Roux-en-Y gastric bypass). An advanced discussion with patients and their families regarding these aspects can help surgeons take the most appropriate course of action in such challenging circumstances.

Another potentially serious issue could be surgery without the knowledge that the patient is pregnant. Though this has implications for all pregnant women and the unborn baby, the implications are even more severe after operations such as bariatric and metabolic surgery[11]. All women in the childbearing age group should, therefore, be offered a routine urine pregnancy test at preassessment to rule out pregnancy[12].

Additionally, laparoscopic surgery may be challenging in a patient who has previously undergone an open abdominal operation especially an emergency laparotomy. In these patients, safe access to the peritoneal cavity may be difficult[8]. Surgeons should generally try to avoid areas where intra-abdominal adhesions are

likely to be maximum for pneumoperitoneum and first port insertion. For example, authors would suggest optical pneumoperitoneum in left upper quadrant as the entry point in patients who have had a previous midline laparotomy.

Like any other surgery, non-urgent procedures may be deferred to allow for patient optimisation. This may include treatment of underlying co-morbidities, smoking cessation, or assisted weight loss. Similarly, patients with obesity could be offered appropriate liver shrinking diet to facilitate cholecystectomy and bariatric procedures [13].

Procedure selection

Over the last couple of decades, an increasing variety of operations are being performed laparoscopically[14-16]. In many cases, the laparoscopic approach has become the norm. For instance, it is difficult to believe that gastric bypass for obesity was once performed using an open approach. A similar expansion of laparoscopy is also being observed in emergency surgery in haemodynamically stable patients[17,18] Laparoscopy has also been reported to be safe with reduced risks of nontherapeutic laparotomy and mortality in patients with blunt abdominal trauma[19]. Though its role in penetrating abdominal trauma is less clear, some surgeons believe it may be useful as a screening tool for identifying patients who would require laparotomy[20]. Procedures can be laparoscopic (such as gastric bypass for morbid obesity), or hybrid-combined open and laparoscopy (such as anterior resection for rectal cancer) depending on the underlying pathology and experience of the surgeon.

Review of pre-operative investigations

The main drawbacks of laparoscopic surgery are reduced tactile and depth perception, which could be critical in many surgical procedures (*e.g.*, segmental colectomy for small malignant polyps)[21]. Where feasible, we suggest endoscopic procedures for such lesions and, if surgery is required, preoperative endoscopic tattooing could help intraoperative identification of the pathology[22,23]. A preoperative review of radiological imaging with an experienced radiologist can also be helpful.

PERI-OPERATIVE CONSIDERATIONS

Team brief and safe surgery checklist

A good and effective team brief is crucial before any operation. All members of the team including the consultant surgeon, surgical assistants/trainees, anaesthetist, anaesthetic trainee/operating department practitioners, scrub nurse, and circulating nurse should be present during the team brief. These sessions provide an opportunity for discussion of any anticipated difficulties, measures for prophylaxis of venous thromboembolism, antibiotic prophylaxis, glycaemic control, patient allergies, patient warming, patient positioning, location of the screen, need for X-ray, *etc.* We strongly recommend team briefings are done as part of the World Health Organisation (WHO) "safe-surgery" checklist, which has been shown to reduce human error and adverse effects while improving communication and teamwork[11,24]. While discussing allergies, particular attention should be paid to allergies to something that would normally be used during or after surgery. Some elective procedures may need to be deferred while patient is referred to appropriate specialists for further testing and confirmation of allergies.

Patient positioning

Proper patient position is essential for the safe performance of laparoscopic surgery. Appropriate precautions must be taken to ensure neutral positioning of major joints and padding of pressure points[25,26]. Some surgeons prefer a "French" position (surgeon stands between the legs of the patient) whereas others prefer standing on the right side of the patient. Regardless of these preferences, basic principles of positioning remain the same. The patient must be secured with a strap over the chest/thighs with or without footrests (depending on whether reverse Trendelenburg position is anticipated during the surgery) to avoid lateral and caudal slippage[11]. Likewise, for pelvic surgery, the patient may need to be in Trendelenburg position. In these cases, hips and knees should be kept in a neutral position in secured leg supports with soft cushions for all pressure points. Shoulder supports can also help prevent cephalad sliding of patients. If stationary retractors are required, such as Nathanson's liver retractor, they should be fastened securely to the operating table to minimise intra-operative adverse events, such as liver injuries[27]. One should use utmost care while

introducing and removing these retractors. The liver may be densely adherent to underlying vascular structures and careless lifting may lead to traction injuries. Moving the patient on and off the operating table should be carried out properly to avoid patient and staff injuries especially for patients with obesity where air mattresses (such as HoverMatt®, HoverTech International, Allentown, PA, United States) may be useful[28].

Laparoscopy setup

A significant number of laparoscopic surgeons suffer from work-related musculoskeletal injuries (up to 70%)[29], and as such ergonomics are more pertinent to laparoscopic surgery than probably open or even robotic surgery. The patient's position, height of the operating table, port position, and laparoscopic monitor setup are some of the important factors to consider in this regard[30,31]. One key suggestion is that the surgeon, the operating field, and the monitor should be in a straight line with triangulation between the camera and main operating ports. The height of the monitor should be just below the surgeon's eye level (preferably 0 to 150) to avoid sprain due to prolonged neck extension[32,33]. Fatigue amongst the surgeon and assistant may increase the risk of error during the procedure, and hence every effort should be made to improve ergonomics. To overcome some of these ergonomic challenges, modern laparoscopic theatre suites are equipped with permanently installed ceiling suspended multiple flat-screen monitors with adjustable inclination[34]. Relative lack of depth perception (2D view) has been a major disadvantage with laparoscopy compared to open surgery. To overcome this, 4K ultra high definition technology[35] and 3D laparoscopic technology have been introduced[36], and several trials have compared the two[35,37]. Neither seems superior to the other, and a recent consensus statement from the European Association of Endoscopic Surgeons concluded that further robust research is required to investigate the avantages of 3D laparoscopy system[38]. Higher cost as well as the stress of the 3D laparoscopy system and issues with surgeon's vision mean that these systems are not yet in widespread usage[39].

Port positioning and insertion techniques

It has been suggested that up to 50% of major complications in laparoscopic surgery occur at the time of port insertion[4]. Surgeons should, therefore, be proficient with different techniques for establishing pneumoperitoneum. Open Hasson technique[40], closed Veress needle entry (named after Janos Veres)[41] and optical ports (with or without prior pneumoperitoneum using a Veress needle) are the most common methods currently used. A recent Cochrane review showed none of these approaches stand out in terms of complications such as visceral injuries and major vascular injuries[42]. However, open Hasson's method is associated with the least chance of entry failures compared to the other two modalities[42]. Even though many surgeons have a preferred technique, the selection of entry technique should probably be based on patient characteristics. For example, the open juxta-umbilical approach is safe and quick for thin to averagely built patients with less abdominal wall fat and with no previous midline laparotomy; whereas optical port insertion in left upper quadrant (with or without prior Veress needle pneumoperitoneum) might be safer for patients with previous midline laparotomy or obesity[43]. In any closed technique, the first port should always be introduced using optical guidance and left upper abdomen (Palmer's point) is regarded to the safest place for this purpose by many surgeons[44].

The size of the primary port (10-12 mm or 5 mm) also depends on the surgeon's preference and type of surgery. For example, some surgeons prefer a 5 mm primary port for paediatric patients to minimise tissue trauma. However, the quality of the picture obtained through a 5 mm scope can be inferior to a standard 10 mm scope due to fewer optical fibres. The size and position of subsequent ports depend on the operation and anticipated instruments in use. Most of the instruments can be safely used through 5 mm ports, but staplers, large clip applicators, retrieval graspers usually require 12 mm ports. Surgeons should also bear in mind that a curved needle will not go through a 5 mm port whereas a ski-shaped needle will. Curved needles can be lost intra-abdominally in an attempt to retrieve them through a 5 mm port[11]. Surgeons should always follow any needle during insertion and removal from the abdominal cavity. Occasionally, larger 15 mm ports are required for thick stapler devices as well as to extract large specimens. However, in the authors' experience, this is rare as most specimens can be removed through a 12 mm port site with some stretch. However, if a 15 mm port is used, the port site should always be closed irrespective of the patient's body mass index. All subsequent port placements, after the primary port insertion, should be under direct vision to avoid injury to the underlying viscera. Injury to inferior epigastric vessels is reported to be the commonest cause of

port site bleeding[45,46]. In thin patients, transillumination can help reduce the chance of inadvertently injuring these vessels.

There are two types of trocars: Bladed and non-bladed that are available for subsequent port placements. The data on comparing the two types are very limited, but non-bladed trocars are probably associated with less trocar-site bleeding with no difference in visceral injury[47]. It is our view that surgeons should only use blunt-tipped non-bladed trocars in laparoscopic surgery as they are less likely to result in inadvertent injuries to epigastric vessels and viscera. All ports should be placed according to the triangulation principle for the better ergonomics[48]. After all the ports are inserted, a gross inspection of the peritoneal cavity is important to identify any inadvertent injury or any unexpected finding. Standard laparoscopic ports are 100 mm in length and suitable for most regular laparoscopic procedures. However, extra-length (150 mm) ports may be necessary to gain access to patients with thick abdominal walls. Usage of appropriate length ports helps to prevent repeated port displacement and fascial injury caused by repeated insertions. If available, balloon tip ports can prevent port displacement.

Pneumoperitoneum

Optimal pneumoperitoneum is vital for safe laparoscopic surgery to ensure adequate visualisation. But, it can also have adverse effects especially on the cardiovascular system[49-51]. Good communication with the anaesthetist is important at the start of insufflation. The rate of insufflation and intra-peritoneal pressure are the key considerations for each procedure[52]. A rapid rise in IAP rise could result in hemodynamic instability from bradycardia or other life-threatening cardiac arrhythmias especially in elderly patients and those with pre-existing cardiac disease[49,50,53,54]. An initial slow rate of insufflation especially at the beginning of the procedure could minimise such events. IAP > 12 mmHg is considered intra-abdominal hypertension with adverse effects on the cardio-respiratory system mainly due to diaphragmatic splinting and carbon dioxide-induced hypercarbia[52].

As a general rule, the lowest possible IAP should be maintained, and an IAP > 15 mmHg is very rarely required. Additionally, good abdominal wall relaxation could improve surgical view[50]. The patient's position could further exaggerate these adverse effects of pneumoperitoneum. For example, in the Trendelenburg position, pressure of viscera on the diaphragm can lead to a reduction in the functional residual capacity[50,51].

Safe handling of the camera

The camera is the eye of the surgeon! Compared to old low-resolution scopes, modern laparoscopes provide high-resolution images enabling the smooth performance of complex and delicate procedures[55,56]. The assistant holding the camera is responsible for providing a clear, focused image to the surgeon. It is important that the assistant knows operative steps and ideally also, the manoeuvres unique to each surgeon. Appropriate training and experience are key to this[57]. The camera is located at the tip of the scope with a fixed angle ranging from 0° to 70°[53], and some with flexible tip allow complete 0 to 180° visualization (LTF-V2 Deflectable Tip Laparoscope, Olympus America Inc., Melville, New York). The familiarity of these angles is important for assistants. Additionally, the camera holder must try to keep the surgical field in the centre of the screen with minimal turbulence.

Sharp instruments such as a diathermy hook and scissors should be followed with the camera during insertion and withdrawal to avoid any inadvertent injuries to the viscera. Before usage, white balancing should be done to achieve a digital image with true colours. White surfaces, such as clean swabs reflect the light enhancing the image, while dark surfaces such as blood, absorb the light and compromise the view. Therefore, the assistant must try to avoid blood-stained and reflective surfaces. The surgeon at the same time should attempt to keep the surgical field tidy. Fogging is a common problem in laparoscopy especially at the beginning of the procedure due to the temperature difference between cold scope and warm peritoneal cavity. Pre-warming with warm water[58-60] or liquid scope warmer (WarmORTM, The O.R. Company, Antioh, TN, United States), anti-fog solutions (FREDTM, United States Surgical, North Haven, CT) are some of the options available for preventing fog formation.

The high intensity of the light can generate significant heat at the tip of the laparoscope. This can burn the drapes and even skin of the patient if due care is not taken.

Instruments in laparoscopy

Correct selection and proper usage of laparoscopic instruments are vital for safe performance of laparoscopic surgery. Describing all laparoscopic instruments is out of the scope of this article. However, we would like to highlight some of the key aspects of commonly used instruments. Tissue graspers, laparoscopic scissors, clip applicators, needle holders, staplers, and suction devices are some of the commonly used instruments in laparoscopic practice. Choice of the instrument depends on multiple factors such as nature of the tissue (delicate *vs* tough), characteristics of the instrument (traumatic *vs* non-traumatic), expected function (dissection *vs* retraction). For example, tissue graspers can be traumatic or non-traumatic depending on the surface characteristics of the jaw blades of the force used by the surgeon. Maryland's forceps are a traumatic device, which should not be used to handle delicate structures such as the small or large intestine. Instead, Johan's non-traumatic forceps should be used for the bowel. It is worth bearing in mind that even atraumatic graspers can lead to tissue trauma if not handled gently. Similarly, Maryland's forceps are useful for blunt dissection and hold tissues (such as bleeding vessels) with their pointed tips. Sharp instruments such as laparoscopic scissors and diathermy hook should always be used under direct vision. Articulated instruments offer "robot-like dexterity" with an improved degree of freedom at lower cost[61,62]

Special instruments

Laparoscopic staplers of appropriate length and staple height should be used depending on the tissue[63-65]. Although modern tri-staplers are shown to be safe and robust, utmost care should be exercised with attention to detail[66,67]. The surgeon needs to be familiar with the type of stapler they are using, and also have good working knowledge of different type of cartridges. Before firing a stapler in Upper Gastro-Intestinal (UGI) surgery, a routine check and communication with the anaesthetist are mandatory to avoid inadvertently catching the orogastric tube or temperature probe, or nasogastric tube within the stapler. All of these have has been reported as never events[68]. Routine use of nasogastric tubes and temperature probes should be avoided, especially in UGI surgery.

Powered staplers and flexible stapler devices (ECHELON FLEXTM, Johnson and Johnson, United States) have also shown some promising results in laparoscopic surgery[69,70]. For most operative procedures (including most bariatric surgery) standard length instruments are adequate. However extra-long instruments may be needed in some patients with severe obesity[71]. Surgical procedures requiring access to gastro-oesophageal junction such as hiatal hernia repair or bariatric surgery require a liver retractor. Different types are available and can be used based on the surgeon's preference and availability (Nathanson Liver Retraction System, Cook® Medical, United States and PretzelFlex Surgical Retraction System, Surgical Innovations, United Kingdom). However, utmost care is required to avoid tissue injury especially to the liver[27,72,73]. Laparoscopic ultrasound, yet another useful tool especially in hepato-pancreatic and biliary operations can be helpful to localise lesions and reduced the incidence of complications[74-76]. More recently, use of Indocynanine Green for fluorescence-guided laparoscopic surgery has shown some initial promising results in hepatobiliary surgery, colorectal surgery, and surgical oncology. It can be useful in tumour localisation, lymph node mapping, and intra-operative angiography as well as cholangiography[77-79]. However, the protocols and technique need to be standardised and validated with further research.

Energy devices in laparoscopy

Modern energy devices have facilitated the progress and development of laparoscopic surgery. Monopolar diathermy is the most basic energy device used in current practice utilised commonly for tissue dissection and haemostasis through hook or Maryland's forceps. Compared to other devices, monopolar diathermy is known to cause significant lateral thermal spread, which requires cautious application close to delicate structures such as the bowel[80,81]. Additionally, inadvertent injuries due to cracked insulation, capacitance coupling due to the usage of metal or hybrid ports are other complications associated with monopolar diathermy[82-84]. Regular inspection and usage of plastic ports are effective means of preventing these potentially disastrous complications. The authors recommend avoiding metal ports for this reason. Surgeons or other team members can also accidentally step on the cutting pedal during the procedure as pedals are on the floor and often hidden under the drapes. We recommend reducing the default cutting setting down to zero as it is rarely needed during routine laparoscopic surgery.

Bipolar diathermy is often a safe alternative when monopolar diathermy is risky *e.g.* close to delicate tissues due to minimal lateral thermal spread or is contraindicated *e.g.* patients with cardiac pacemakers[74]. Several advanced energy devices are available and utilise different technology[80,85]. LigasureTM (Medtronic Technologies, Dublin, Ireland) uses bipolar energy with pressure to seal blood vessels up to 7 mm. HarmonicTM (Ethicon technologies, Raritan, NJ, United States), and SonoSurgTM (Olympus Technologies, Tokyo, Japan), use high-frequency ultrasonic waves to generate heat, thereby causing tissue coagulation and dissection with significantly lower lateral thermal spread compared to monopolar devices[80]. These devices can be safely used even in patients with cardiac pacemakers, in whom monopolar diathermy is contraindicated[86]. During usage, the active blade of these devices should be kept under direct vision to prevent any inadvertent injury to underlying tissues. Studies demonstrate heat at the tip of the device can lead to temperatures as high as > 100 °C and can last up to 20 s after usage[87]. Therefore, tip contact with vulnerable tissues should be avoided immediately after usage and surgeons should allow some time for it to cool down before using again. ThunderbeatTM (Olympus Technologies, Tokyo, Japan) is another device that combines both high-frequency ultrasonic waves and bipolar diathermy, which allows tissue dissection as well as sealing of vessels up to 7 mm[88]. Energy devices related burns may not be immediately apparent and result in late perforations with disastrous consequences[89,90].

Tissue dissection in laparoscopy

Tissue dissection in laparoscopy can be a challenging task even for experienced surgeons due to a relative lack of haptic feedback. Laparoscopic scissors are often used for sharp dissection, whilst advanced energy devices could be used where tissues are expected to bleed. Pointed tip devices such as Maryland's forceps are useful to open-up the tissue planes. Suction devices or laparoscopic pledgets can also be used to create tissue planes[91].

Haemostasis in laparoscopy

Any discrete bleeding vessel should be identified, isolated, and properly controlled before proceeding to the next step of the procedure. Diathermy is the most frequently used modality for haemostasis and is advocated for a capillary-sized vessel. Laparoscopic clips or Hem-o-lok® (Teleflex®, Morrisville, NC, United States) ligating clips are indicated for defined, named vessels. For larger vessels such as a splenic artery or ileocolic pedicle, we suggest using either locking clips *e.g.*, Hem-o-lok® (Teleflex®, Morrisville, NC, United States) or vascular staplers (1.0 mm to 2.0 mm Endo GIATM, Medtronic, Minneapolis, United States, and Ethicon, Johnson & Johnson Medical, Belgium).

Bleeding from raw or inflamed tissue *e.g.*, liver bed after a difficult cholecystectomy or pelvis during rectal resection can be difficult to control[91-93]. These can sometimes be controlled with topical haemostatic agents such as gelatins, collagens, thrombin, and fibrin sealants (BioGlue®, Cryolife Inc., Kennesaw, GA, United States), and synthetic glues[94,95]. Some of these agents *e.g.*, Surgicel (Ethicon, Johnson & Johnson Medical, Belgium) can cause an intense inflammatory reaction, and lead to the formation of an abscess[96-99]. Occasionally, ligating or transfixing the pedicle with sutures provides the most secure control. We believe all laparoscopic surgeons should be able to carry out laparoscopic suturing. All energy devices can cause injury to nearby structures due to lateral thermal spread and as such, it is vital to keep the instrument completely under vision during use[80,85]. Once metal clips are applied, further diathermy should be avoided as it causes shrinkage of tissues underneath with subsequent loosening and slippage of the clip, and the metal clip could lead to the spread of the diathermy current to adjacent tissue causing thermal injury[82,83,100].

Laparoscopic suturing and anchoring

Laparoscopic suturing is an essential skill for all laparoscopic surgeons. Selection of correct needle size, length of the suture, proper handling of the needle at various angles are vital considerations for safe laparoscopic suturing. Additionally, pre-prepared laparoscopic knots with loops (ENDOLOOP®, Johnson & Johnson Medical, Belgium) are commercially available as a quick option for certain procedures as laparoscopic appendicectomy. Specific anchoring devices (such as ProTackTM, Medtronic Ltd., United Kingdom, and Securestrap®, Johnson and Johnson Medical, Belgium) can be used for mesh fixation during a laparoscopic hernia repair. However, they can be associated with complications such as chronic pain or erosions[101,102]. More recently, absorbable tackers have been introduced in an attempt to reduce the

odds of these complications (AbsorbaTackTM, Medtronic Ltd., United Kingdom).

Timeouts during the procedure and second opinion

Laparoscopic surgery can be physically and mentally demanding for the surgeon and could easily lead to fatigue and errors[103,104]. We recommend short breaks during long or difficult procedures for the whole team. If the operation is not progressing as expected, a second opinion from and experienced colleague could be invaluable[105]. Surgeons should not regard conversion as a failure.

Final check

Towards the end of the procedure, surgeons should ensure adequate haemostasis and check for any inadvertent bowel injury. We also recommend ensuring adequate blood pressure and reducing the pressure while checking for haemostasis. A haemostasis check with low blood pressure and high-pressure pneumoperitoneum may be falsely reassuring.

Surgeons should consider closing all internal defects and 15 mm port sites. Most 10-12 mm port sites should also be closed except in patients with severe obesity where many surgeons do not recommend closing blunt 10-12mm port sites especially when ports have been angled during placement[106,107]. After the withdrawal of ports, all port sites should be checked for bleeding and adequate haemostasis must be ensured. Surgeons should finally check the operating count with nurses and do a proper "time out" to ensure all planned procedures have been performed. The operating count should include surgical specimens and specimen retrieval bags as it is not uncommon during laparoscopic surgery for surgeons to leave a specimen/retrieval bag intraabdominally during the surgery for later removal[11]. At the end of the procedure, we recommend a mental pause for the surgeon to reflect on the procedure – especially consider if all planned procedures have been performed; all foreign bodies such as tonsil swabs, retrieval bags, removed previously placed foreign bodies such as gastric bands, and specimens have been removed; and all ports that needed closing have been closed.

POST-OPERATIVE CONSIDERATIONS

Laparoscopic surgery has transformed post-operative care and reduced the length of in-hospital stay to the extent that many surgical procedures can be undertaken as day cases[108,109]. This is probably because of minimal physiological disturbances and stress with laparoscopy[110]. Early discharge is beneficial for patients and should be routine after in-hospital care is no longer needed.

Analgesia

Pain management plays a vital role in recovery post-laparoscopy as in any other type of surgery. We recommend effective multi-modal analgesia[111] following any laparoscopic surgery including the infiltration of long-acting local anaesthetic agents at port sites. Deep breathing exercises and chest physiotherapy can reduce respiratory complications[112].

Thromboprophylaxis

Appropriate thromboprophylaxis is crucial for laparoscopic surgery because of the higher IAP[113]. A recent study by our group identified failure to prescribe the correct thromboprophylaxis as one of the commonest serious clinical incidents after bariatric surgery[11]. A combination of mechanical and pharmacological thromboprophylaxis should be used. We recommend continuing to use the calf compression devices in the immediate post-operative period till the patient is ambulatory, and compression stockings even after discharge till the patient has resumed near-normal levels of mobility. Low molecular weight heparin is an effective pharmacological thromboprophylaxis usually started preoperatively and continued for variable duration post-operatively for those at highest risk.

Enhanced recovery after surgery

We would strongly advocate incorporating an Enhanced Recovery After Surgery (ERAS) programme[114-116]. For certain specialties and procedures, separate ERAS protocols have been developed[117-120].

Table 1 Summary of various safety considerations throughout the patient journey when undergoing a laparoscopic procedure

Stage of surgery	Safety considerations	
Pre-operative	Patient selection	Rule out pregnancy for elective procedures in women of child bearing age group
		Optimisation of risk factors
	Procedure selection	Elective surgery
		Emergency general surgery
		Abdominal trauma
	Pre-operative investigations	Supplementary procedures (*e.g.*, endoscopic tattooing)
		Review of radiological investigations
Intra-operative	Before start	Effective communication and surgical check list
		Ensure correct patient, correct procedure, correct site
		Consider allergies, antibiotic prophylaxis, DVT prophylaxis, and glycaemic control
		Safe and appropriate patient positioning
		Ensure comfortable and effective laparoscopy set-up
	During surgery	Safe pneumoperitoneum and ergonomically favourable port positioning
		Use lowest possible pneumoperitoneum pressure
		Accurate selection and handling of instruments (*e.g.*, camera, energy devices)
		Meticulous tissue dissection and haemostasis
		Regular evaluation of operative steps
		Low threshold for seeking second opinion
	At the end of the surgery	Check for haemostasis with reduced intra-abdominal pressure and adequate blood pressure
		Proper closure of port sites
Post-operative	Early recovery	Multimodal analgesia
		Thromboprophylaxis
		Clear plan for oral intake and patient's routine medications
		Use Enhanced Recovery Protocols for elective surgery
	Complications	Early recognition of warning signs and prompt intervention
		Tachycardia not reliable as an early warning sign for patients on Beta blockers
		Appropriate training of nursing staff and early escalation. Use Early Warning Scores
	Discharge advices	Clear discharge documentation for patient and their primary care doctor
		Patient education on complications and anticipated recovery times

DVT: Deep vein thrombosis.

Management of diabetes

Poor perioperative glycaemic control is shown to be associated with increased infection rate and mortality across many surgical specialties[121-123]. Therefore, it is highly recommended to have a strict policy for peri-operative glycaemic control, especially in patients on insulin[124].

Patient's routine medications

Many patients admitted for elective surgery may be on regular medications for a variety of medical conditions, which may need to be withheld peri-operatively. Incorrect management of patients' regular medications[12] can lead to avoidable harm [125]. Close collaboration with physicians, pharmacists, and specialist nurses can help. For medications that are commonly omitted perioperatively such as antiplatelets and anticoagulants, it is good practice to have clear local perioperative guidelines/ protocols, to minimise errors. Surgeons should clearly document when these can be

restarted safely after surgery and in what dosages in their operation notes. It is equally important to ensure patients' regular medications such as antihypertensives are prescribed correctly especially in the post-operative period. A thorough review by a pharmacist at pre-assessment and/or on the ward after surgery can help prevent these errors.

Post-operative complications and management

It is important to ensure that the junior doctors and nursing staff are appropriately trained to identify a complication early. Tachycardia is often the first sign of an unwell patients. However, its limitations as an early warning sign in patients who are on Beta-blockers should be understood. Shoulder tip pain and port site pain are frequently reported after laparoscopic surgery. Diaphragmatic irritation due to retained carbon dioxide can trigger referred pain to shoulders, which can last up to a few days post-operatively[126-128].

Overall, laparoscopic surgery is associated with reduced abdominal pain and discomfort. Surgical teams should take excessive pain and regular use of opiate analgesia more than 24 h after surgery seriously. Such a patient could be developing an early complication such as bowel perforation or bile leak after cholecystectomy and a Computed Tomography scan may be falsely negative[129]. We recommend having a low threshold for re-laparoscopy.

Discharge advice

Surgical teams should provide clear information to patients and their carers about the expected recovery times after surgery. They should also be advised regarding warning symptoms and who to contact in such cases. This is crucial as laparoscopy has reduced the length of stay in the hospital, and patients will usually be home when complications develop. Unwell patients should have rapid access to senior surgical input during the early postoperative period.

CONCLUSION

This review presents some of the key considerations in the safe performance of laparoscopic surgery. We have attempted to summarise them in Table 1 for readers. Many of our recommendations are based on experience and need to be examined scientifically. There is also a need for consensus-building amongst experts in this crucial area of patient safety.

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MINIREVIEWS

Endoscopic cryotherapy: Indications, techniques, and outcomes involving the gastrointestinal tract

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Abstract

Endoscopic cryotherapy is a technique utilized for the ablation of target tissue within the gastrointestinal tract. A cryotherapy system utilizes the endoscopic application of cryogen such as liquid nitrogen, carbon dioxide or liquid nitrous oxide. This leads to disruption of cell membranes, apoptosis, and thrombosis of local blood vessels within the target tissue. Several trials utilizing cryotherapy for Barrett's esophagus (BE) with variable dysplasia, gastric antral vascular ectasia (GAVE), esophageal carcinoma, radiation proctitis, and metastatic esophageal

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carcinomas have shown safety and efficacy. More recently, liquid nitrogen cryotherapy (cryodilation) was shown to be safe and effective for the treatment of a benign esophageal stricture which was refractory to dilations, steroid injections, and stenting. Moreover, liquid nitrogen cryotherapy is associated with less post procedure pain as compared to radiofrequency ablation in BE with comparable ablation rates. In patients with GAVE, cryotherapy was found to be less tedious as compared to argon plasma coagulation. Adverse events from cryotherapy most commonly include chest pain, esophageal strictures, and bleeding. Gastric perforations did occur as well, but less often. In summary, endoscopic cryotherapy is a promising and growing field, which was first demonstrated in BE, but the use now spans for several other disease processes. Larger randomized controlled trials are needed before its role can be established for these different diseases.

Key Words: Cryotherapy; Gastric antral vascular ectasia; Barrett's esophagus; Esophageal cancer; Palliative therapy

Core Tip: Cryotherapy involves freeze-thaw cycles of tissue to eradicate problematic lesions such as Barrett's esophagus with variable dysplasia, gastric antral vascular ectasia, radiation proctitis, esophageal carcinomas and metastatic esophageal carcinomas. Two of the most used cryotherapy systems involve liquid nitrogen and carbon dioxide. Cryoballoon focal ablation system is another system, but not widely available. Cryotherapy systems have shown efficacy for these conditions even in patients who were refractory to the current standards of care.

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INTRODUCTION

Endoscopic cryotherapy is a technique utilized for the ablation of target tissue within the gastrointestinal (GI) tract. A cryotherapy system utilizes the endoscopic application of cryogen such as liquid nitrogen or liquid nitrous oxide to the target tissue leading to disruption of cell membranes, apoptosis, and thrombosis of local blood vessels. Endoscopic cryotherapy first showed success in the treatment of Barrett's esophagus (BE), but over time has been used for both treatment and symptomatic relief of many disease processes throughout the GI tract. This review will discuss the current and future roles of cryotherapy in GI endoscopy.

MECHANISM OF ACTION

Cryotherapy achieves tissue destruction *via* two mechanisms, which include both immediate and delayed effects, while simultaneously preserving the cryo-resistant structures. The initial effect of cryotherapy is the formation of ice crystals by freezing the intracellular and extracellular water in the tissues. The ice crystals lead to the disruption of the cell membranes and protein denaturation. This creates an osmotic gradient, which draws water from the intracellular compartment leading to the cell dehydration and destruction[1-3]. The degree of cell death is similar to other modalities which are heat based like radiofrequency ablation (RFA) or argon plasma coagulation (APC) but this method preserves the architecture of the underlying tissue and the extracellular matrix which reduces scarring[1]. Cellular death of peripheral tissues that does not occur from direct injury by cryoablation may eventually die *via*

apoptosis, caused by activation of cytochrome C due to the mitochondrial injury[4,5].

The thawing process follows the initial freezing mechanism[6]. During this phase, there is fusion of intracellular ice crystals, with the maximum effect occurring at -20-degrees-C to –50-degrees-C, which further damages the cell membranes. In addition, there is an indirect injury to the vascular endothelium *via* the fusion of ice crystals resulting in tissue necrosis and ischemia, due to the platelet aggregation, thrombus formation and regional hyperemia[7-9]. The risk of perforation in cryotherapy is decreased as collagen and elastin fibers are cryo-resistant as compared to the epithelial cells[10,11].

TYPES OF ENDOSCOPIC CRYOTHERAPY METHODS

Currently, the two types of endoscopic cryotherapy methods which are commercially available include liquid nitrogen cryotherapy and carbon dioxide (CO_2) cryotherapy.

Liquid nitrogen cryotherapy

In this technique, a contact-free low-pressure spray of liquid nitrogen is delivered through a 7F catheter and reaches a temperature of -196-degrees-C, which freezes the GI mucosa (Figure 1). During this process, the catheter and the endoscope experience a rapid drop in temperature and become less compliant, which makes it difficult to operate the endoscope and/or move the catheter in the biopsy channel[2,12]. As nitrogen gas expands at room temperature, it leads to rapid cooling due to the Joule-Thompson effect (rapid expansion of a gas leading to a change in temperature of a gas). To warm the cryoprobe, the depressurized gas can be vented out and a heating circuit within in the catheter is necessary to maintain pliability of the device[2,13].

Prior to liquid nitrogen cryotherapy, a 20 F dual-channel decompression oral-gastric tube is placed to allow for both active and passive gas venting to reduce the risk of GI perforation[14]. This is utilized because after the liquid nitrogen spray freezes the tissue, the warmth transforms it into nitrogen gas, which expands at a rate of 6-8 L in a 20 s liquid nitrogen spray[15]. During the procedure, the abdomen is frequently examined by palpation, usually by an assistant, to ensure adequate decompression and to alert staff if distention is recognized[16].

CO_2-based cryotherapy

In this technique, a compressed CO_2 gas spray is applied through a catheter with a 0.005-inch diameter tip opening. The CO_2 gas reaches a temperature of -78-degrees-C and is delivered at a rate of 6-8 L/min at a pressure of 450-750 psi[14]. A suction cap is placed on the distal end of the endoscope which is connected to the CO_2 evacuation system, and this allows venting of the CO_2 gas build up to avoid distention[14,17]. The CO_2 gas is vented simultaneously as cryotherapy is being delivered. Unlike liquid nitrogen cryotherapy, a heating circuit is not necessary since the endoscope and the catheter delivering the CO_2 gas are not at risk of freezing[12].

Differences between liquid nitrogen cryotherapy and CO_2 based cryotherapy: Several differences exist between liquid nitrogen cryotherapy and CO_2 cryotherapy systems aside from the type of gases and temperatures utilized. Both systems can cause abdominal distension as the cryogen changes to a gaseous state, however, this is less problematic with the CO_2-based system because of a low-profile catheter which evacuates the excess CO_2. Both systems have issues with fogging of the endoscope lens, which compromises visualization. The CO_2 based system is comparatively cheaper and can be stored at room temperature as compared to the liquid nitrogen system, which requires storage in expensive containers to maintain a temperature between 195.8-210-degrees-C[12,18].

Duration and dosage of cryotherapy: Cryotherapy involves two stepwise processes: Freezing and thawing, often performed in cycles. The amount of tissue injury caused by cryotherapy depends on the rate and duration of cooling, the number of freeze-thaw cycles, and the distance from the target tissue to the origin of the spray. A critical limitation of cryotherapy is that dosimetry data for this technology is lacking, and is, for all intents and purposes, largely unknown. Initial dosing regimens on BE patients consisted of 3 cycles of 20 s each, which was changed to 4 cycles of 10 s each after over distention in a Marfans syndrome patient led to a gastric perforation. The clinical experience suggests that freeze times of 10-15 s may be efficacious for short term in ablation of BE[19].

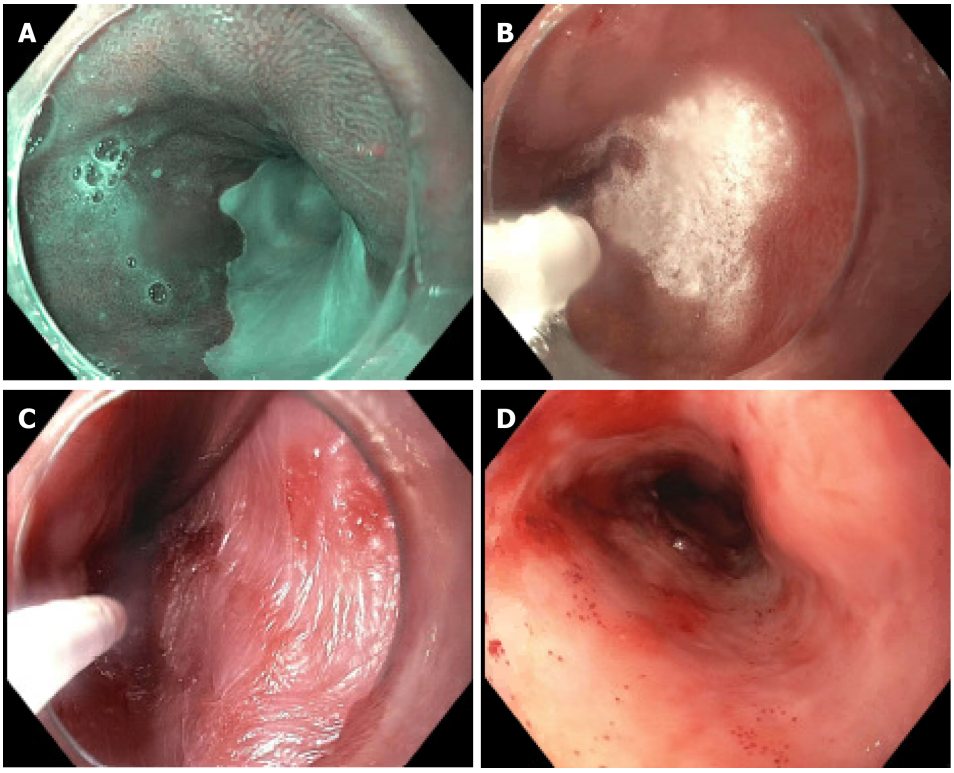

Figure 1 Liquid nitrogen cryotherapy for Barrett's esophagus. A: Long segment Barrett's esophagus pre-cryotherapy intervention under narrow band imaging; B: Application of liquid nitrogen cryotherapy in Barrett's esophagus; C: Crystallization post cryotherapy in Barrett's esophagus; D: Post cryotherapy changes seen in Barrett's esophagus.

In a study performed in a porcine animal model, the CO_2 system demonstrated a dose-dependent effect on tissue damage based on seconds of CO_2 spray. A 15 s spray caused minimal necrosis, a 30 s spray caused damage to the submucosa and a 120 s spray caused damage to the muscularis propria[20]. In another porcine study, liquid nitrogen was sprayed for 10-60 s and did not appear to show a dose-dependent effect on tissue[21]. This emphasizes how poorly the technology is understood.

Despite our poor understanding of dosimetry, the varying doses of cryotherapy used to date have shown efficacy with an acceptable safety profile in clinical settings. It is believed that longer freeze times maybe needed for the palliative treatment of esophageal cancer. There is limited data describing the clinical outcomes to compare the various freeze durations and number of freeze-thaw cycles[19].

UTILITY OF CRYOTHERAPY IN VARIOUS GI ETIOLOGIES

BE

BE, first described in 1950 by Dr. Norman Barrett, a British thoracic surgeon, refers to replacement of normal squamous epithelium of the esophagus by columnar epithelium, at least 1 cm above the gastro-esophageal junction, and is a precursor lesion of esophageal adenocarcinoma (EAC)[22]. Although the incidence of BE is increasing in the western world, the risk of EAC in patients with BE is now estimated to be at least 10 fold higher when compared to the general population[23].

BE is traditionally classified based on endoscopic length of salmon colored mucosa, as long segment BE (LSBE > 3 cm) or short segment BE (SSBE < 3 cm). However, the diagnosis of BE needs histological correlation in addition to endoscopic appearance, which takes into account replacement of esophageal squamous epithelium by columnar epithelium along with presence of goblet cells, a marker of intestinal metaplasia (IM)[22].

Endoscopic ablative techniques remain the treatment of choice for BE patients with dysplasia and/or early esophageal cancer without lymphatic spread[24]. The available endoscopic ablative techniques include RFA, photodynamic therapy and cryotherapy. RFA combined with endoscopic mucosal resection (EMR) has become the standard treatment for BE because of its demonstrated efficacy, cost effectiveness, and better

side effect profile[25]. For limited surface areas, APC and bipolar probes are a less expensive alternative compared to cryotherapy. However, these procedures may have higher BE recurrence rates[13,26,27].

Liquid nitrogen cryotherapy in BE: A pilot study of liquid nitrogen cryotherapy published in 2005 reporting on only 11 patients with BE and variable dysplasia achieved complete endoscopic and histologic eradication in 82% of patients[28]. A subsequent multi-center study of 77 patients utilizing liquid nitrogen cryotherapy therapy for BE high grade dysplasia (HGD), BE dysplasia, and BE IM achieved complete eradication at rates of 94%, 88% and 53%, respectively. Additionally, complete remission of intramucosal cancer and carcinoma was seen in all 7 patients. The most common adverse event (AE) was chest pain at 17.6%. Three patients developed a stricture which was successfully managed endoscopically with dilation. Gastric distention from liquid nitrogen therapy led to a perforation in a patient with Marfan's syndrome[29].

A recent study by Ramay *et al*[30] looked at the efficacy of liquid nitrogen cryotherapy on BE-HGD and intramucosal adenocarcinoma (IMC). This study included 50 patients who were analyzed over 3 years and 40 patients who were analyzed over 5 years. The initial rates of complete remission of HGD, dysplasia, and IM were 98%, 90%, and 60% and were found to be comparable at 3 and 5 years. Incidence rates of recurrent IM, dysplasia, and HGD/EAC on follow-up after initial complete eradication of IM were 12.2%, 4.0%, and 1.4% per person-year for the 5-year cohort.

Cryotherapy ablation compared against RFA for BE: A recently published non-inferiority trial comparing RFA with liquid nitrogen cryotherapy in 31 patients with HGD and early adenocarcinoma found similar results between the two groups. Complete remission of BE in patients undergoing RFA *vs* liquid nitrogen was 21% *vs* 12%, respectively. Pain scores were significantly lower in the liquid nitrogen cryotherapy group as compared to the RFA group. There was no major procedure related AEs. These results are preliminary as we are awaiting results of the complete trial[31]. Similar findings were demonstrated in a different study regarding lower post procedure pain scores in those undergoing liquid nitrogen cryotherapy as compared to RFA[32].

A retrospective study with 154 patients were treated for Barrett's dysplasia, IM or HGD with either RFA or liquid nitrogen cryotherapy. Complete remission of HGD was comparable between both groups at 88%. Complete remission of IM was more successful in RFA *vs* cryotherapy (67% *vs* 41%) and statistically significant. Complete remission of dysplasia was also comparable between RFA *vs* cryotherapy (88% *vs* 79%) [33]. Similar results were also seen in a recent retrospective study by Fasullo *et al*[34] which included 100 patients in the RFA group and 62 patients in the liquid nitrogen cryotherapy group.

Cryotherapy has several potential advantages over RFA, which include fewer complications (pain, stricture), cost effectiveness and a no contact technique. Disadvantages of cryotherapy include the following: abdominal distention due to gas, difficulty in visualization during the endoscopic procedure due to freezing of tissue and barotrauma, poor dosimetry, and limited outcome data compared to RFA.

CO_2 cryotherapy in BE: Data to establish the durability of CO_2 cryotherapy as a treatment for BE is limited. In a single center study of 64 patients with BE reported complete remission of IMC, HGD and IM in 77%, 94% and 55% of patients, respectively[35]. This was the largest study demonstrating the safety and long-term efficacy results of CO_2 cryotherapy and the results were comparable to that seen with liquid nitrogen cryotherapy[35].

According to a small single center prospective case series of 10 patients, a negative experience led to an early termination of a study due to an insufficient effect of CO_2 cryoablation in BE and early neoplasia. Most patients underwent EMR prior to cryotherapy. Complete remission of IM and dysplasia in 9 patients was reported to be 11% and 44% at the 6 mo follow up, respectively. Two noteworthy AEs included gastric perforation and esophageal laceration[36].

Cryoballoon focal ablation system using nitrous oxide for BE: A cryoballoon-based system is the most recent developed endoscopic cryotherapy system and ablates mucosa *via* direct contact of an inflated balloon tip catheter filled with nitrous oxide [14,37]. The balloon reaches temperatures close to -80-degrees-C[38]. The device has been slow to achieve widespread commercial release.

In a study published the same year by Sawas *et al*[39], 42 patients underwent cryoballoon focal ablation system (CbFAS) of which 37 had unsuccessful prior BE treatments indicating a more challenging cohort. Complete remission of dysplasia and IM were achieved in 54.8% and 9.5% of patients over a mean follow up period of 7.5 ± 5.7 mo.

A multicenter non-randomized comparative study of 46 patients utilizing CbFAS *vs* RFA showed comparable outcomes (88% *vs* 90%) for SSBE regression. There were 20 patients in the CbFAS group and 26 in the RFA group. Peak pain and duration of pain was reported to be significantly lower in the CbFAS group[40].

Canto *et al*[41] recently published a large multicenter trial on 120 patients of which 45% had previously received EMR for BE. The rates of complete remission of dysplasia and IM rates in 94 patients who have completed 12 mo of follow up are 97% and 91%, respectively. Fifteen patients developed strictures, which were treated with dilation. Three other patients developed serious AEs: 1 perforation after stricture dilation, 1 deep laceration after dilation, and 1 upper GI bleed. So far BE has not been seen on follow up biopsies post CbFAS. This is the largest trial to date representing the efficacy of CbFAS for BE.

Outcomes regarding this technique are variable and require confirmation by further studies. There are a few clinical trials being conducted for CbFAS effect on BE and we await their results.

CbFAS compared to liquid nitrogen cryotherapy for BE: Recently, a retrospective study compared cryoballoon therapy to liquid nitrogen cryospray. Forty-six patients were treated with CbFAS and 25 were treated with liquid nitrogen cryospray. They reported the complete eradication rates of dysplasia and IM to be comparable at 95.6% *vs* 96% and 84.75% *vs* 80% in the cryoballoon group *vs* liquid nitrogen cryospray group, respectively. Strictures were reported in 4 of the cryoballoon patients and 3 of the cryospray patients, which were treated with dilation. The authors reported cryoballoon to be more convenient since it uses cartridges prefilled with nitrous oxide as compared to handling a large nitrogen tank. In instances where patients had a large hiatal hernia, needed to be treated in a retroflexed position, or required a large surface area to be targeted, liquid nitrogen cryospray was used instead[37].

Gastric antral vascular ectasia

Gastric antral vascular ectasia (GAVE), also known as 'watermelon stomach', is an uncommon cause of GI bleeding but can often cause clinically significant chronic and severe bleeding. The prevalence of GAVE is estimated to be 0.3% in a large endoscopic series and 4% in highly selected cohorts for obscure GI bleeding. It is often misdiagnosed as antral gastritis and can be difficult to differentiate from portal hypertensive gastropathy[42,43]. Majority of patients with GAVE become transfusion dependent despite iron supplementation[43,44]. The best approach for the treatment has not yet been identified but the standard treatment in most countries is endoscopy based. APC has been a preferred treatment, however, can be very labor intensive due to the large surface area covered and multiple sessions required. Moreover, patients can develop recurrence overtime and may become transfusion dependent[45]. Cryotherapy is another intervention that has been utilized for GAVE, but the data is limited.

The etiology of GAVE is poorly understood however the histopathology demonstrates specific abnormalities involving mucosa and lamina propria[44]. It is commonly associated in patients with cirrhosis, renal disease, cardiac disease and autoimmune disease such as scleroderma[46]. There are 4 alterations seen: Vascular ectasia of mucosal capillaries, focal thrombosis, spindle cell proliferation and fibrohyalinosis consisting of homogenous substance around the ectatic capillaries of lamina propria[42]. By utilizing cryotherapy, superficial necrosis of the mucosa and submucosa occur followed by re-epithelialization[12].

CO_2 based cryotherapy for GAVE: In a single center pilot study by Cho *et al*[47], 12 patients with GAVE received 36 CO_2 based cryotherapy treatments with complete response in 50% and partial response in 50%. Eight patients in this cohort had prior unsuccessful APC treatments of which 6 had complete response after CO_2 based cryotherapy. There were no immediate cryotherapy related complications. Some late complications seen on follow up endoscopy included bleeding from a disrupted Schatzki's ring and minor scarring/ulceration in the gastric antrum.

CbFAS with nitrous oxide for GAVE: In a pilot study of 7 patients, complete eradication was seen in 71% after undergoing CbFAS with nitrous oxide. All patients had undergone laser, thermal and APC intervention previously without success. No major AE occurred related to cryotherapy[48]. In another study of 23 patients utilizing

CbFAS, 83% of patients were transfusion independent and 87% had more than 75% eradication of their GAVE at 6 mo[46]. Similar result was reported in a case report using CbFAS in a patient with GAVE who had failed previous treatment with APC [49].

Cryotherapy for GAVE has seemingly promising results but has limited data and requires further investigation with larger trials. One major advantage of cryotherapy in comparison to APC is that it can treat larger surface areas in a shorter amount of time.

Radiation proctitis

One of the most frequent complications after radiation therapy for pelvic malignancies is radiation proctitis[50,51]. The consensus has been that the incidence is related to the dose of radiation, exposure area, delivery method and the use of cytoprotective agents. The dose for most treatments is 45-50 Gy and up to 90 Gy. Complications are less for doses from 45-70 Gy, but doses above 70 Gy cause significant long-standing damage. Depending on the type of radiation therapy used, the incidence for proctitis varies from 1% to as high as 39%[50].

Radiation proctitis can be acute or chronic. Acute proctitis is an inflammatory process occurring within 3 mo of the initial therapy and is usually self-limiting after the radiation treatment has stopped. The treatment of acute proctitis is generally supportive with hydration, anti-diarrheal, steroids or 5-aminosalicylic acid enemas. Chronic proctitis on the other hand, can start during the acute phase of radiation but symptoms do not become obvious until the treatment is stopped around a median of 8-12 mo[52,53]. The treatment for chronic proctitis involves non-invasive methods such as anti-inflammatory agents, sucralfate, short-chain fatty acids, hyperbaric oxygen, antioxidants, or more invasive methods such as ablation and surgery. Invasive methods are reserved for refractory symptoms that have failed medical management. The ablation methods involve formalin, endoscopic coagulation with APC, yttrium-aluminum-garnet laser or potassium titanyl phosphate laser, cryotherapy, bipolar electrocoagulation, and hyperbaric oxygen[50,51,54,55]. Surgery carries the risk of morbidity and mortality[56]. APC has shown to be an effective and safe treatment for chronic proctitis with success rates of 80%-95% for bleeding cessation, but controlled trials are lacking[51,57,58]. Complications from these therapies may result in deep tissue injuries like ulcerations, perforation and fistulas, whereas cryotherapy has the potential to avoid these problems since the ablation of the mucosa is superficial[57].

CbFAS with nitrous oxide for radiation proctitis: In a small pilot study of 7 patients who underwent nitrous oxide cryotherapy, 100% resolution of lower GI bleeding was observed with no major AE. All patients had previous unsuccessful treatment with APC[48].

Liquid nitrogen cryotherapy for radiation proctitis: In a small prospective study of 10 patients who underwent liquid nitrogen cryoablation, the rectal telangiectasia density improved in 70% and the symptom severity scores improved in 80%. Cecal perforation due to gaseous overdistention occurred in 1 patient and was managed surgically. Rectal ulceration occurred in another patient, which improved from conservative management[57]. Similar results were seen in another small prospective study of 10 patients. There were no major complications[55].

Differences between APC and cryotherapy for radiation proctitis: Best results with APC have been achieved in mild to moderate radiation proctitis but its role has been limited for severe disease. Cryotherapy on the other hand has shown efficacy in patients with refractory chronic radiation proctitis[59]. Utilization of APC as compared to cryotherapy can be very time consuming, require bowel preparation to reduce the risk of perforation and may require multiple sessions. Cryotherapy can also be carried out with little or no sedation[55]. Larger studies need to be conducted to validate these findings and to determine the role of cryotherapy in acute and chronic radiation proctitis.

Squamous cell carcinoma and adenocarcinoma of esophagus

Treatment of symptoms: Dysphagia can be a debilitating symptom in patients with inoperable esophageal carcinoma. Further, it can lead to malnutrition and significant decrease in overall quality of life. Currently the two most common palliative treatments included radiation therapy or esophageal stent placement[60]. These methods may have advantages, but their disadvantages can impair quality of life as well.

In a case series of 49 patients with inoperable malignant dysphagia, 120 liquid nitrogen cryotherapy sessions were conducted, and overall dysphagia scores had improved. Minor AEs were seen in 5% with one patient developing a dilation-related perforation[60]. Cryotherapy may be an alternative treatment option for improving dysphagia with minimal side effects in esophageal carcinoma, however larger studies are needed.

Treatment of EAC and squamous cell cancer: Globally, squamous cell carcinoma of the esophagus comprises 80% of all esophageal carcinomas. These patients have a poor prognosis, however, if diagnosed at the stage of squamous cell neoplasia, then curative endoscopic therapy can be performed. Currently, there is limited data assessing its overall effectiveness.

Cryoballoon focal ablation with liquid nitrous oxide for esophageal cancer: In a prospective trial from China of 80 patients, CbFAS was utilized in patients with one flat intraepithelial neoplasm that was less than 6 cm. Complete eradication occurred in 90% after a single treatment. At the one-year mark, 97% had complete eradication and one had a persistent moderate grade intraepithelial neoplasia. Self-limiting lacerations of the mucosa occurred in 3 patients and no strictures developed[61]. Cryotherapy with CbFAS seems promising, but further studies are needed.

Liquid nitrogen cryotherapy for esophageal cancer: Cash *et al*[62] had described a 73-year-old male with stage 3 squamous cell carcinoma of the esophagus who was not a candidate for radiation therapy or surgery, and he achieved complete remission for 24 mo after treatment with liquid nitrogen cryotherapy. The patient did develop a significant stricture, which required several dilations, steroid injections, and temporary stenting.

Tsai *et al*[63] conducted a prospective study utilizing liquid nitrogen cryotherapy in patients with EAC. Eighty-eight patients were analyzed with stages T1a-T2. Complete eradication rates in patients with T1a and T2 were 76.3% and 6.7%, respectively. The most common side effect was stricture and developed in 13.6% of patients. Cryotherapy may be of benefit for treatment in early disease.

Another study done by Ramay *et al*[64] utilized liquid nitrogen cryotherapy for palliation in patients with both invasive adenocarcinoma and squamous esophageal carcinoma. At fifty months, 50% (26) of patients remained alive after treatments. There were few AEs including hematemesis in one patient and stricture formation in 3 with 2 requiring dilations. Overall this method may be a viable treatment palliative treatment option, however larger scale studies are needed.

Survival benefits in metastatic disease: Beyond treatment, another study assessed the impact on overall survival in patients with metastatic esophageal carcinoma. This study retrospectively studied 83 patients with stage IV metastatic esophageal cancer. Thirty-nine patients received chemotherapy alone and 44 patients received chemotherapy and palliative liquid nitrogen cryotherapy. All patients that underwent treatment with cryotherapy had malignant dysphagia. The median overall survival was 19.2 in cryotherapy with chemotherapy and 9.5 mo in with chemotherapy alone. This study demonstrated that cryotherapy might have survival benefits for patients with metastatic esophageal cancer. While the etiology for this is unknown, the authors of the study postulated that cryotherapy can improve dysphagia and thus nutritional status[65].

The role for cryotherapy in palliative treatment of esophageal carcinoma and symptomatic improvement is promising however larger scale studies are needed.

Other uses for cryotherapy

Liquid nitrogen cryotherapy followed by dilation (cryodilation) has been utilized in benign tracheal strictures and stenoses by pulmonologists and thoracic surgeons with improved airway narrowing. Recently a case report described its use in a patient with a benign refractory esophageal stricture who had previously undergone an esophagectomy for an EAC. The patient underwent 7 procedures with liquid nitrogen cryotherapy followed by dilation. Each procedure incorporated 20 s of cryotherapy and 60 s of thaw time for a total of 3 freeze-thaw cycles followed by stricture dilation to 18 mm. The patient's dysphagia had improved, and weight loss was no longer an issue. This procedure was useful in a patient with refractory esophageal stricture, however its role has yet to be established and further randomized controlled trials are needed to evaluate its safety and efficacy in a larger population[66].

CONCLUSION

Endoscopic cryotherapy is a promising and growing field. First demonstrated in BE, the use now spans from cancer treatment to symptomatic improvement in GAVE. Most studies done have been on small populations. Large scale randomized control studies are needed to determine the overall effectiveness and utility of endoscopic cryotherapy in treatment of various GI disorders. The ease of use and the ability for relatively safe and noninvasive procedures makes it a very promising modality for the future.

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MINIREVIEWS

Is gastroscopy necessary before bariatric surgery?

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Abstract

Obesity is the abnormal accumulation of fat or adipose tissue in the body. It has become a serious health problem in the world in the last 50 years and is considered a pandemic. Body mass index is a widely used classification. Thus, obese individuals can be easily classified and standardized. Obesity is the second cause of preventable deaths after smoking. Obesity significantly increases mortality and morbidity. We thought of preparing a publication about routine procedures for the preoperative evaluation of obesity. The question that we asked as bariatric and metabolic surgeons but which was not exactly answered in the literature was "Is esophagogastroduodenoscopy (EGD) necessary before bariatric surgery?" We found different answers in our literature review. The European Association of Endoscopic Surgery guidelines recommend EGD for all bariatric procedures. They strongly recommend it for Roux-en-Y gastric bypass (RYGB). As a result of a recent study by the members of the British Obesity & Metabolic Surgery Society, preoperative EGD is routinely recommended for patients und-ergoing sleeve gastrectomy, even if they are asymptomatic, but not recommended for RYGB. It is recommended for symptomatic patients scheduled for RYGB. According to the International Sleeve Gastrectomy Expert Panel Consensus Statement, preoperative EGD is definitely recommended for patients scheduled for sleeve gastrectomy, but its routine use for RYGB is controversial. However, a different view is that the American Society for Gastrointestinal Endoscopy recom-mends endoscopy only for symptomatic patients scheduled for bariatric surgery. In the literature, the primary goal of EGD recommended for sleeve gastrectomy has been interpreted as determining esophagitis caused by gastroesophageal reflux. In the light of the literature, it is stated that this procedure is not necessary in America, while it is routinely recommended in the European continent. Considering medicolegal cases that may occur in the future, we are in favor of performing EGD before bariatric surgery. In conclusion, EGD before bariatric surgery is insurance for both patients and physicians. There is a need for larger and prospective studies to reach more precise conclusions on the subject.

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Core tip: The European Association of Endoscopic Surgery guidelines recommend esophagogastroduodenoscopy (EGD) for all bariatric procedures. They strongly recommend it for Roux-en-Y gastric bypass (RYGB). The British Obesity & Metabolic Surgery Society recommends routine perioperative EGD for sleeve gastrectomy (SG), even if patients are asymptomatic, but not for RYGB. It is recommended for symptomatic patients scheduled for RYGB. According to the International Sleeve Gastrectomy Expert Panel Consensus Statement, preoperative EGD is definitely recommended for SG, but its routine use for RYGB is controversial. The American Gastrointestinal Endoscopy Association recommends that endoscopy be performed only on symptomatic patients scheduled for bariatric surgery.

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INTRODUCTION

Obesity is the accumulation of excess fat in the body. It is defined by body mass index (BMI). BMI is calculated by dividing body weight in kilograms by the square of height in meters. It is an easy and practical method. Obesity is a serious global public health problem and is considered a pandemic. It is the second most common preventable cause of death after smoking[1-5].

According to the data of the World Health Organization, it is predicted that in 2030, approximately 60% of the world's population will be affected by and 1.1 billion people will be obese[6]. It has been reported that the prevalence of obesity in Turkey has increased in parallel with that in other European countries and has reached high rates of 37% of overweight individuals and 36% of obese individuals[1]. Obesity causes more than 700 billion dollars of health expenditure globally every year.

Studies such as waist-to-hip ratio, skinfold thickness, bioelectrical impedance analysis, computed tomography, magnetic resonance imaging, dual energy radiographic absorptiometry, and air densitometry are used to define obesity[2,4,7-9].

The etiology of obesity is multifactorial. Genetic and environmental factors are diverse.

Obesity is a disease that is difficult to treat. It is necessary to follow step by step the treatment algorithm. The first step includes healthy eating and lifestyle changes. Exercise is added to the first step treatment in second-line therapy. Behavioral changes are added to the third-line treatment. In the fourth-line treatment, additional drug therapy is added to these. Surgical treatment remains the only option for patients who fail despite all these treatments.

Surgery is not completely safe and can cause fatal complications. The disadvantages of drug treatments are the high number of undesirable side effects, limited effects, and rapid weight gain when patients stop taking drugs[10,11]. The aim of surgical treatment is to reduce morbidity and mortality due to obesity. Providing long-term permanent weight loss with bariatric surgery reduces the metabolic effects of obesity and increases survival. Bariatric surgery can reduce > 50% of excess weight. Compared to nonsurgical methods, surgery causes more effective and permanent weight loss in the long term. In a study conducted by Çoşkun *et al*[12], it was shown that in obese patients who underwent gastric bypass, it provided a 16.4 kg/m^2 reduction in BMI in 1 year.

Today, it is generally accepted that bariatric surgery is the most effective and permanent method used in the treatment of obesity. Studies on bariatric surgery have been carried out and clear information and algorithms about which surgical procedure to choose for which patient, postoperative complications and what should be

Table 1 Benefits of gastroscopy before bariatric surgery

Possible finding	Effect
Detection of gastroesophageal reflux disease	Selection of surgical technique
Evaluation of esophagitis	Selection of surgical technique
Evaluation of gastric mucosa (with biopsy result)	Selection of surgical technique
	Selection of stapler to be used
Evaluation of gastric outlet obstruction	Selection of surgical technique
	Prediction of additional procedure
Helicobacter pylori test	Treatment plan
Detection of possible malignancy	Canceling the surgery
Polyp excisions	Postponing the surgery until the pathology result
Detection of alkaline reflux gastritis	Selection of surgical technique
	Treatment planning
Detection of hiatal hernia	Selection of surgical technique
	Prediction of additional procedure

considered when dealing with them, and postoperative diet and follow-up issues have been created by various centers. However, this is not the case for preoperative preparation. Routine preoperative examinations are performed in obese patients before each operation.

The main theme of this article is esophagogastroduodenoscopy (EGD), which is part of the gastrointestinal evaluation before bariatric surgery. Our aim is to clarify whether routine EGD examination is necessary before bariatric surgery. In our clinic, we perform routine EGD in all patients before bariatric surgery and colonoscopy in patients who need it.

However, while discussing in the article, we made an independent evaluation in the light of the literature, except for our practice.

IS GASTROSCOPY NECESSARY BEFORE BARIATRIC SURGERY?

Routine preoperative EGD screening is controversial in patients undergoing bariatric surgery. There are surgical societies that recommend and do not recommend routine EGD screening to detect suspected gastric lesions/findings. To begin with, we should state the views of two separate associations.

The European Association of Endoscopic Surgery guidelines recommends EGD for all bariatric procedures, and strongly recommends it for Roux N-Y gastric bypass (RNYGB)[13]. The American Gastrointestinal Endoscopy Association recommends endoscopy only for symptomatic patients scheduled for bariatric surgery[14].

Schigt *et al*[15] stated that the standard preoperative evaluation of EGD in bariatric patients is not indicated because a high number of patients need to be screened to find clinically significant abnormalities. Gómez *et al*[16] identified age > 55 years and gastroesophageal reflux disease as risk factors on endoscopy screening. They concluded that although abnormalities are common in preoperative EGD, they rarely change the surgical treatment technique due to these findings. Due to the poor correlation between patients' complaints and endoscopic findings, routine preoperative endoscopy may be useful in detecting both lesion and inflammation[17-19].

Schlottmann *et al*[20] reported that 29.4% of asymptomatic patients were found to have abnormal findings by EGD.

The rate of conditions such as hiatal hernia, gastritis, or esophagitis detected during preoperative EGD of a patient who will undergo bariatric surgery with or without symptoms is as high as 62%–67%. Preoperative EGD is important before bariatric surgery[21]. Malignant findings are not commonly detected by EGD in patients undergoing bariatric surgery. For example, Wolter *et al*[22] in a study of 801 patients, found that malignancy was observed in 0.5% of all patients. D'Hondt *et al*[23] found two cases of distal adenocarcinoma in the esophagus during preoperative EGD in 371

patients with gastric banding. Praveenraj *et al*[24] did not find malignant lesions during EGD in 613 bariatric patients. However, they reported a case of low-grade gastric-mucosa-associated lymphoid tissue lymphoma after histopathological evaluation of tissue biopsies.

Wolter *et al*[22] recommends performing routine endoscopy before bariatric surgery to predict possible malignant lesions. Mihmanli *et al*[25] in their series of 157 cases, reported that one case changed the operation type as a result of preoperative endoscopic examination. Gómez *et al*[16] have changed only 1.7% of surgical operation types in routine bariatric preoperative endoscopy.

The results of histopathological examination of the excised gastric sample can give information about the prevalence of malignant cases, especially after laparoscopic sleeve gastrectomy (LSG). In a meta-analysis of 48 different articles, it was reported that the rate of total surgical procedures ranged from 4% to 7.8%. According to the pathology results of all cases, malignancy was found in 0.4%[26].

Yormaz *et al*[27] studied 232 patients and argued that performing preoperative EGD would decrease postoperative complications. They talked about the importance of EGD findings in surgery selection. They recommended preoperative EGD to only symptomatic patients.

A recent study of Members of the British Obesity & Metabolic Surgery Society found that 10% of clinics dealing with bariatric surgery in the UK considered preoperative EGD to be completely unnecessary, and 31% showed that they included it in their routine preoperative evaluations. Important findings were detected in 23% of the patients scheduled for SG. As a result, the British Obesity & Metabolic Surgery Society recommends EGD routinely in the preoperative period, even if patients undergoing SG are asymptomatic, but not for RNYGB. They recommend RNYGB to planned symptomatic patients[28].

It is important to determine esophagitis with gastroesophageal reflux as the main purpose of EGD recommended for SG. It is estimated that sleeve gastrectomy in such patients worsens the situation and increases the risk of cancer in the long term[29]. Already, according to the International Sleeve Gastrectomy Expert Panel Consensus Statement, severe esophagitis and Barret esophagus are contraindications for SG[30]. Therefore, preoperative EGD is definitely recommended for patients who are planned to undergo SG. In contrast, routine use of RNYGB is controversial.

Mihmanlı *et al*[25] retrospectively evaluated 157 patients who underwent EGD before bariatric surgery (SG or RNYGB) between March 2013 and March 2015. They obtained abnormal findings in 67% of these patients. Only 17% of these patients were symptomatic cases. EGD findings classified 54% of gastritis, 10% of esophagitis, 17% of hiatal hernia, 5% of gastric ulcer, and 3% of other cases. *Helicobacter pylori* was positive in 62% of the patients.

Mazahreh *et al*[31] prospectively evaluated 219 patients scheduled for LSG, and 1 year later, all individuals were evaluated for the presence of symptomatic gastroesophageal reflux disease, and no significant difference was found between the two groups, so they stated that they did not require routine EGD. Gastric biopsy was performed on 148 patients. Chronic inflammation was found in 65%, inflammatory activity in 32%, and intestinal metaplasia in 2%. While endoscopic findings caused the operation to be delayed in 54% of the patients, it caused the surgical procedure to be changed in one patient due to the heterotopic pancreatic tissue. Mihmanlı *et al*[25] showed that more than half of the obese patients (54%) had a disease that required perioperative treatment (67%) and recommended EGD before bariatric surgery.

While EGD is not routinely recommended before bariatric surgery in the American continent, it is recommended in the European continent. In cases where it is not possible to see the remaining part of the stomach such as mini-gastric bypass, it is useful to make the final evaluation of the stomach.

Performing EGD in a patient with no complaints has negative aspects in terms of time, cost, and any complications that may develop during the procedure. Of course, the advantages of this process are too many to ignore, such as the capture of a premalignant or malignant lesion. It will provide early diagnosis and treatment. It will improve the patient's quality of life.

The cost–benefit analysis of routine EGD in each patient may also be a matter of debate, which naturally will increase the cost of this procedure.

CONCLUSION

EGD before bariatric surgery is an insurance for both patients and physicians. When

endoscopy is used perioperatively, it will be more comfortable to use preoperatively. Unfortunately, a missed case of stomach tumor can incur a great cost. This is also life-threatening. Benefits of gastroscopy before bariatric surgery are summarized in Table 1. Larger and prospective studies are needed to yield more precise results on the subject. Regional, national and international associations should create an algorithm on this issue within a short time. Thus, a worldwide standard should be provided for health care. An end must be found to these long-running discussions.

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MINIREVIEWS

Current role of endoscopic ultrasound in the diagnosis and management of pancreatic cancer

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Abstract

Endoscopic ultrasound (EUS) has emerged as an invaluable tool for the diagnosis, staging and treatment of pancreatic ductal adenocarcinoma (PDAC). EUS is currently the most sensitive imaging tool for the detection of solid pancreatic tumors. Conventional EUS has evolved, and new imaging techniques, such as contrast-enhanced harmonics and elastography, have been developed to improve diagnostic accuracy during the evaluation of focal pancreatic lesions. More recently, evaluation with artificial intelligence has shown promising results to overcome operator-related flaws during EUS imaging evaluation. Currently, an appropriate diagnosis is based on a proper histological assessment, and EUS-guided tissue acquisition is the standard procedure for pancreatic sampling. Newly developed cutting needles with core tissue procurement provide the possibility of molecular evaluation for personalized oncological treatment. Interventional EUS has modified the therapeutic approach, primarily for advanced pancreatic cancer. EUS-guided fiducial placement for local targeted radiotherapy treatment or EUS-guided radiofrequency ablation has been developed for local treatment, especially for patients with pancreatic cancer not suitable for surgical resection. Additionally, EUS-guided therapeutic procedures, such as celiac plexus neurolysis for pain control and EUS-guided biliary drainage for biliary obstruction, have dramatically improved in recent years toward a more effective and less invasive procedure to palliate complications related to PDAC. All the current benefits of EUS in the diagnosis and management of PDAC will be thoroughly discussed.

Key Words: Endoscopic ultrasound; Contrast-enhanced harmonic; Elastography; Artificial intelligence; Radiofrequency ablation; Celiac plexus neurolysis; Biliary drainage

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Core Tip: Endoscopic ultrasound (EUS) is currently an essential tool in the diagnostic work-up and treatment of pancreatic cancer. Contrast-enhanced harmonics, elastography and artificial intelligence provide additional information in the evaluation of focal pancreatic lesions to improve diagnostic accuracy during EUS evaluation. Interventional EUS has dramatically improved the palliative treatment of patients with pancreatic cancer, basically for local ablation therapies, adequate pain control with celiac plexus neurolysis and EUS-guided biliary drainage for the treatment of biliary obstruction.

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INTRODUCTION

Pancreatic cancer is a serious oncological condition with a very poor outcome and survival. Pancreatic ductal adenocarcinoma (PDAC) is the most frequent pancreatic cancer, which represents 85% of the pathological diagnoses[1]. It is the 14th most common cancer and has the 7th highest cancer-related mortality in the world[2], and it has the fourth highest mortality in the United States[3]. The incidence is increasing, mainly in the Western world. It is predicted to increase to the second most common cause of cancer-related death in the United States and Western Europe by 2030[4]. The 5-year survival rate is very low, ranging from 2% to 9%. The most important factor that influences survival is tumor stage at diagnosis, although only 20% of patients are candidates for surgical resection at the time of diagnosis[5,6]. Its indolent clinical presentation, proximity to major vessels and absence of accurate serum markers and imaging modalities for early diagnosis are features that complicate early detection and screening for this severe disease. However, an accurate histological diagnosis and proper staging are essential in the treatment strategy of pancreatic cancer.

Multidetector computed tomography (MDCT) is the mainstay imaging technique for the evaluation of solid pancreatic lesions suggestive of potential PDAC, not so much for adequate characterization of the lesion as for accurate staging of potential malignant disease[7]. Preoperative evaluation for surgical resectability is currently based on MDCT staging[8]. Magnetic resonance imaging (MRI) is also an interesting imaging modality, but it does not reach the accuracy of MDCT with regard to resectability and particular vascular involvement[9].

Endoscopic ultrasound (EUS) was introduced in the 1980s as a high-precision tool for the analysis of the gastrointestinal wall and adjacent structures. High-quality images that have dramatically improved over time and the proximity of the transducer to the pancreatic parenchyma make EUS an invaluable tool for the description of pancreatic parenchyma and, thus, for pancreatic cancer diagnosis and staging.

The performance of EUS has been compared with that of computed tomography (CT) for pancreatic cancer staging. A meta-analysis did not find any difference in determining tumor resectability when these two techniques were compared[10]. However, rapid and recent progress in CT technology and the ability to review CT scan imaging studies during multidisciplinary meetings for treatment planning make CT the method of choice for initial staging and subsequent follow-up. In contrast, EUS has a higher sensitivity for the detection of solid pancreatic tumors, mainly for lesions under 2 cm in diameter, when compared with CT and MRI[11]. Hence, EUS is the preferred imaging technique for the screening of pancreatic cancer in high-risk populations[12]. Due to the benefits of EUS imaging provides in pancreatic cancer evaluation, many additional technological tools have been developed in recent years to try to improve the quality of EUS imaging and increase the diagnostic accuracy of this technique. In addition, the availability of large working channel linear array probes, or "therapeutic EUS scopes", has opened a new range of possibilities beyond tissue acquisition for an accurate pathological diagnosis. It is also highly useful for therapeutic interventions, mainly for the palliation of pancreatic cancer-associated

symptoms or to deliver targeted local treatment. The role of EUS in the evaluation and treatment of pancreatic cancer will be thoroughly discussed.

ANCILLARY EUS IMAGING TECHNIQUES FOR PANCREATIC CANCER EVALUATION

Contrast-enhanced harmonic EUS

Contrast-enhanced (CE) harmonic EUS is an ultrasonographic technique that uses a microbubble-based contrast agent (Sonovue™, Sonazoid™ or Definity™, depending on local market availability) to visualize vascularization and perfusion patterns in the liver, pancreatic parenchyma or lymph nodes. This technique was made available for EUS during the late 2000s. Harmonic components of the signal generated by intravenously injected microbubbles improve the evaluation of the microcirculation without Doppler-related artifacts[13]. Two main features are evaluated during contrast evaluation: one is the enhancement of the lesion with the contrast agent, which can be non-, hypo-, iso- or hyperenhancement, and the second is the contrast distribution, which can be classified as homogeneous or heterogeneous. Regarding focal pancreatic lesions, contrast is a useful tool to differentiate pancreatic adenocarcinoma from other focal lesions. Whereas pancreatic adenocarcinoma has a hypoenhanced pattern, other focal lesions, such as neuroendocrine tumors, metastatic lesions and inflammatory diseases, are either iso- or hyperenhanced[14,15]. Two different meta-analyses have shown a pooled sensitivity between 92% and 93% and a pooled specificity between 87% and 88% for the differential diagnosis between pancreatic cancer and other focal pancreatic lesions[16,17]. CE-EUS also plays a role in patients with suspected pancreatic adenocarcinoma, but negative results after EUS fine needle aspiration (FNA), mainly in the setting of chronic pancreatitis, improve biopsy targeting at a second attempt[18,19]. Finally, CE-EUS is an important tool in deciding between surgery or surveillance of focal lesions with a negative or inconclusive histological diagnosis after EUS FNA or FNB. Being an operator-dependent procedure is one of the pitfalls of CE-EUS, but this disadvantage has been counterbalanced by an optimized technique of quantification analysis including a time-intensity curve for the region of interest[20,21].

Elastography

Elastography is an ancillary technique for the endosonographic evaluation of solid pancreatic lesions that evaluates tissue stiffness. There are two different types of elastography, namely, strain and shear wave elastography. However, only strain elastography is available for EUS, which measures tissue distortion after applying a predetermined pressure. Three different elastography measurements are available: The pattern of recognition in which the stiffness is defined by colors in which green represents the normal pancreatic tissue stiffness, blue stands for hard tissue and red represents softer tissue. This measurement is highly operator-dependent and does not provide objective information. The second measure, called the strain ratio, is a method of stiffness comparison between the target area and a reference area in a grayscale image. The distance and the selected area of reference can induce some bias with this technique[22]. Finally, the strain histogram is a computer-enhanced method for dynamic analysis, where color images are transformed into a grayscale of 256 tones. These two latter quantitative measurements provide more objective information than the pattern of recognition color evaluation. Interestingly, a meta-analysis did not show any difference in accuracy between qualitative and quantitative evaluations. It showed a pooled sensitivity of 98% and specificity of 63% for qualitative measurement and a pooled sensitivity of 95% and specificity of 61% for quantitative endoscopic ultrasound elastrography measurement for correct differentiation between malignant and benign solid pancreatic lesions[23]. However, the low specificity of elastography suggests that the stiffness of a lesion is not perfectly correlated with the presence of neoplastic tissue.

Contrast vs elastography

Few studies have addressed this comparison. One of the first studies compared CE power Doppler EUS and EUS elastography[24]. No difference was found between the two techniques regarding sensitivity, specificity or accuracy. A more recent prospective study evaluated this query and found that quantitative elastography had a higher sensitivity than CE-EUS[25]. In this study, the combination of both techniques

did not improve the ability to differentiate benign from malignant solid pancreatic lesions. The addition of CE harmonic evaluation to elastography did not increase the diagnostic accuracy but may have improved the characterization of the pancreatic lesion to differentiate between distinct malignant lesions.

Artificial intelligence

It is well known that the performance of EUS for an accurate diagnosis depends highly on the technical capacity, knowledge and experience of the endoscopist. To overcome this flaw, a strong effort has been made in the development of artificial intelligence (AI) in the evaluation and differential diagnosis of pancreatic lesions[26]. AI is a mathematical prediction technique that recognizes patterns after analyzing data in computer-based programs, performing tasks supposedly mimicking some of the processes of human intelligence. Computer-aided diagnosis (CAD) refers to diagnoses based on image processing by computer programs[27].

The first study using CAD for pancreatic endoscopic ultrasound was reported 20 years ago by Norton *et al*[28], who concluded that digital image analysis of the pancreas is feasible and at least comparable to human interpretation, setting the basis for future AI studies in the field of pancreatic diseases[28]. Subsequent studies have evaluated the performance of AI for the differential diagnosis of pancreatic lesions, with a reported accuracy of 94%[29].

Deep learning techniques refer to more advanced AI algorithms that use deep neural networks to provide high-performance predictions in which computers improve their own performance by taking advantage of previous success and error without further human intervention[30]. Deep learning is used in computer vision for imaging classification. Automatic image feature detection is its most prominent advantage[31]. Few studies have described the use of deep learning for EUS image analysis since its introduction in 2019. One study was designed for IPMN malignancy diagnosis with an accuracy of 94%[32], and another study by Tonozuka *et al*[33] was the first deep learning AI study that evaluated the ability of AI to detect pancreatic cancer. This study showed promising results with a sensitivity of 92.4%, specificity of 84.1%, positive predictive values of 86.8% and negative predictive values of 90.7%[33].

In the future, AI can probably help in the treatment strategy ahead of tissue acquisition or in cases where biopsy is not feasible. AI can also decrease the risk of missing a lesion due to inattention and help in the training process of future endosonographers [34].

INTERVENTIONAL EUS IN PANCREATIC CANCER

EUS-guided tissue acquisition

The mainstay for an accurate diagnosis of pancreatic cancer is based on tissue acquisition. EUS FNA has been the standard method to acquire pancreatic tissue for more than 25 years. Great effort has been made to improve the diagnostic accuracy of FNA. Different changes in the standard technique have been adapted to improve FNA performance. Regarding technical issues, the fanning technique, which involves sampling different areas of the lesion during a single needle pass, can decrease the number of passes needed for an adequate diagnosis and increase the number of patients in which the diagnosis can be achieved at the first attempt. The use of suction during FNA has been reported in a randomized controlled trial to improve diagnostic accuracy[35], but the slow-pull technique in which no suction is applied has also been shown to yield equivalent results with less blood contamination[36]. Finally, the number of passes recommended for a better diagnostic yield is 3 or 4. More than 4 passes have no proven additional benefit[37]. Other technical variations, such as puncture with or without the use of the stylet or the availability of an on-site cytologic evaluation, have provided no significant improvements in the diagnostic yield to ensure adequate EUS tissue acquisition.

A variety of needles with modifications in the type of tip and needle size (diameter) have been manufactured, and their diagnostic performance has been evaluated. Different sizes, from 25G to 19G, were produced to try to improve the sample size and ease of manipulation. No significant difference was seen in sample quality when different needle sizes were compared for solid pancreatic lesions[38,39].

Recently, FNB needles have been made available. One can differentiate two types of FNB needles, namely, fenestrated needles, introduced in approximately 2010, and more recently, "cutting" needles with a bevelless, dented tip. Both types aim to provide core tissue samples. The performance of regular FNA needles with reverse

bevel needles was compared. A randomized controlled trial reported that fewer passes are needed to obtain an adequate sample and better histological diagnosis with reverse bevel needles[40]. Nevertheless, a different meta-analysis showed no significant difference in diagnostic accuracy between these two different needle types[41].

"Cutting" needles provide core biopsy tissue and permit the preservation of cellular architecture, allowing FNB molecular profiles of pancreatic samples to be obtained for personalized oncological treatment. Two different types of "cutting" needles are available: A Franseen needle and a fork-tip needle.

A recent meta-analysis including only randomized controlled trials comparing FNA and FNB for solid pancreatic needles showed comparable results regarding sample adequacy and diagnostic accuracy, with similar sensitivity for both needles (93.1% for FNB and 90.4% for FNA)[42]. One of these studies yielded a higher quality histological sample with the FNB needle when compared with the standard FNA needle, with the former achieving better histological architecture retainment[43] (Figure 1).

Complications due to EUS-guided tissue acquisition have been described in 0.5%-3% of cases, including acute pancreatitis, infection, perforation, and bleeding[44]. Although less frequently, needle tract seeding has also been described. This complication has a prevalence of 0.003%-0.009% with FNA needles, and to our knowledge, only one case of needle tract seeding has been reported with FNB needles [45]. Even though the risk is low, we should be aware of this risk mainly for cases in which surgery is performed, but the needle site of puncture is not within the scope of surgical resection[44,45].

EUS fiducials placement

The only curative option in patients with pancreatic cancer is surgical resection. Unfortunately, only 20% of patients are surgical candidates after adequate diagnostic evaluation and staging[46]. In advanced stages, chemotherapy and radiotherapy can improve survival and quality of life[47]. Image-guided radiotherapy (IGRT) can precisely deliver radiation to the target lesion through real-time advanced imaging guidance to decrease toxicity to surrounding tissue. Stereotactic body radiotherapy (SBRT) is a form of IGRT in which multiple beam radiation allows high-dose radiation therapy to a select location for a precise target treatment[48]. This technique allows adequate control of local disease with a significant decrease in radiation toxicity[49]. To achieve this goal, implantable markers (fiducials) are needed as landmarks for precise radiation delivery. Fiducials are radiopaque markers, usually made of gold, placed in the target lesion to ease accurate radiation treatment. Originally, fiducials were placed either percutaneously or surgically. The former has the limitation of intervening structures in the needle tract, and the latter requires a more invasive procedure. EUS fiducial placement has emerged as a potential alternative to avoid these hurdles. Initially, they were placed with a 19G FNA needle, but due to the stiffness of these needles, smaller fiducials were developed for 22G FNA needle placement. Recently, preloaded needles became available to ease this procedure. A recent meta-analysis evaluated technical aspects of EUS-guided fiducial placement specifically for pancreatic cancer. This study showed an overall technical success rate of 96.27%, a migration rate of 4.33% and an adverse event rate of 4.85%[50].

Radiofrequency ablation

Radiofrequency ablation (RFA) is a local procedure that generates tissue coagulative necrosis induced by high temperature[51]. This is a well-established treatment for solid tumors of the kidney, lung and liver. Recently, an EUS RFA device composed of a specifically designed 19G needle and a purpose-built RF generator was developed to perform RFA treatment under EUS guidance. This technique produces local ablation through thermal coagulation and is also assumed by some authors to stimulate the immune response by the release of antitumoral-specific antigens (also known as the abscopal effect), thus potentially offering two different therapeutic mechanisms[52]. It is important to point out that this latter effect has been adequately described in many reports, but it is a rarely recognized clinical event[53].

As with every invasive procedure, there are potential adverse events, including pancreatitis, pancreatic duct strictures, bowel perforation, bleeding and peritonitis [54]. EUS FRA has recently been evaluated for two indications: one for the local treatment of unresectable pancreatic cancer and the other for neuroendocrine pancreatic tumors unsuitable for surgical resection.

Unresectable pancreatic cancer

RFA for unresectable pancreatic cancer is a safe and feasible procedure. A recent study

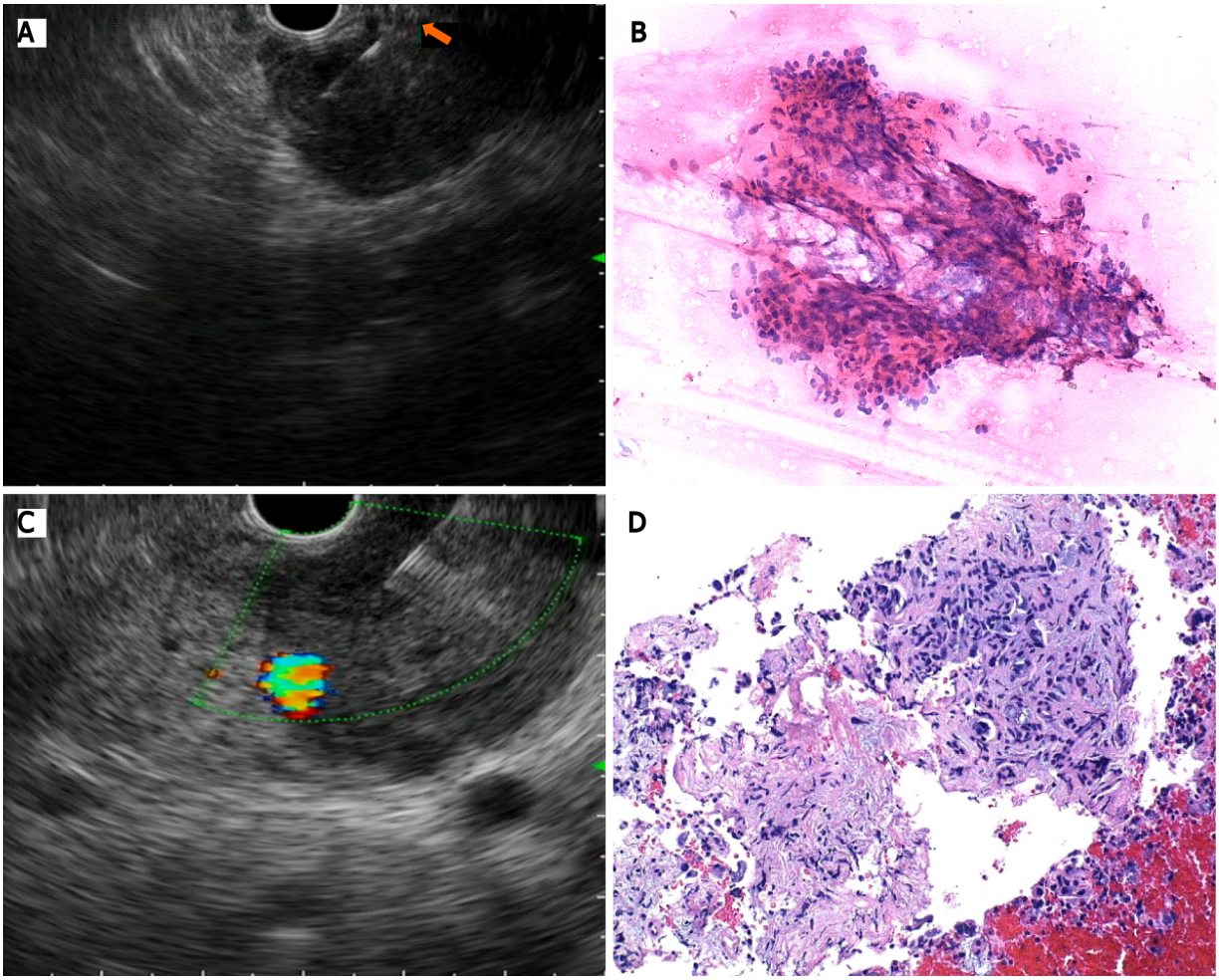

Figure 1 Endoscopic ultrasound-guided tisssue acquisition. A: Puncture with a conventional fine needle aspiration needle; B: Pancreatic adenocarcinoma after cytologic evaluation; C: Tissue acquisition with a Franseen needle; D: Pancreatic tissue with preservation of cellular architecture.

that enrolled 10 patients with unresectable pancreatic cancer reported a technical feasibility of 100% and no major adverse events[55]. To date, none of the published studies have reported any significant efficacy data.

Neuroendocrine tumors

Pancreatic neuroendocrine tumors (NETs) are infrequent tumors (1% of all pancreatic neoplasms) usually exhibiting indolent behavior that occur sporadically or in the context of hereditary multiple endocrine neoplasia (MEN) type 1[56]. Small nonfunctional NETs (diameter under 20 mm) are usually followed with CT, MRI and/or positron emission tomography[57], whereas surgical resection is advised in larger or hormone-producing NETs. Adverse events, such as pancreatic fistula, have been reported in 45% of cases after tumor enucleation and 14% after pancreatectomy[58]. RFA has emerged as a potential treatment option for these cases. Some data have been published in recent years regarding the usefulness of RFA for NET treatment. In a prospective study that evaluated the efficacy of EUS RFA in 12 patients bearing a total of 14 treated tumors, the 1-year complete resolution rate was 86%[59]. The role of RFA has also been described for functional NETs[60]. In a recent meta-analysis, the role of RFA in pancreatic neuroendocrine tumors demonstrated an overall effectiveness of 96% without differences between functional and nonfunctional NETs[61].

Another meta-analysis evaluated this technique for the treatment of different types of pancreatic tumors and showed a technical success of 100%, a clinical success of 91.5% and an overall adverse event rate of 14.6%, where abdominal pain was the most frequently reported[62]. Most available studies that have evaluated this technique are small-sized studies with fewer than 10 patients and uncontrolled protocols. Many different settings of ablation time and energy delivery were used in each study, but this had no impact on the final results. One prospective study evaluated EUS RFA plus chemotherapy *vs* chemotherapy alone for unresectable pancreatic cancer. Even though

there was a decrease in the morphine dose requirement for pain control, no difference was seen regarding survival[63]. Larger multicentric prospective and controlled trials are needed to determine the utility of this potential therapeutic resource in the treatment of pancreatic cancer.

Celiac plexus neurolysis

Endoscopic ultrasound celiac plexus neurolysis was introduced in 1996 for the management of pain caused by pancreatic cancer[64], which is the most common symptom in pancreatic cancer and the main impairment in quality of life of this group of patients. Pain is present in 60% of patients at presentation and in 80% of patients with advanced pancreatic cancer[65]. During celiac plexus neurolysis, absolute alcohol is injected as a neurolytic agent directly into the celiac plexus area to disrupt the transmission of pain signals. Bupivacaine 0.25% is additionally injected as an analgesic agent (Figure 2).

Three techniques have been described: A central technique in which the total amount of the agent is injected at the origin of the celiac artery, a bilateral technique in which the injection is done on both sides of the celiac artery with an equal distribution, and the most recently described direct celiac ganglia neurolysis. A meta-analysis evaluated the efficacy of this procedure, with pain relief being obtained in 72% of patients[66]. Conflicting results have been obtained regarding the best EUS neurolysis technique, but visibility and direct injection of the celiac ganglia substantially increase the response to treatment[67]. Regarding the timing of neurolysis, a randomized controlled trial concluded that early CPN reduces pain and decreases morphine consumption in patients with advanced pancreatic adenocarcinoma[68]. A systematic review described CPN having minimal superiority over analgesic drugs but with fewer adverse effects than opioids[69]. The most commonly described complications associated with CPN are transient and include diarrhea (23%), hypotension (33%) and pain exacerbation (36%)[70]. A mildly higher risk of retroperitoneal bleeding has been described with the bilateral technique[71]. EUS-guided celiac plexus neurolysis is a good option for pain treatment in patients needing high doses of opioids or with important adverse events related to these medications.

EUS-guided biliary drainage

Biliary duct obstruction is one of the main complications related to pancreatic cancer. Endoscopic retrograde cholangiopancreatography (ERCP) with stent placement is the standard treatment to drain biliary duct obstruction. Nevertheless, ERCP fails in 5-7% of the cases[72]. Until recently, percutaneous transhepatic biliary drainage (PTBD) was the most frequent approach for biliary drainage after ERCP failures. Although PTBD has significant morbidity, it is uncomfortable and generally requires more than one procedure[73]. This is why EUS biliary drainage emerged as an option for obstructive jaundice in patients with pancreatic cancer where ERCP fails with similar technical and clinical success compared with PTBD, with a lower incidence of adverse events. The first EUS biliodigestive anastomosis was described in 2001[74]. Since then, many advances in this endoscopic technique have been developed. A meta-analysis reported a technical success rate of 90% and adverse event rate in 17% of patients treated by EUS BD[75]. EUS biliary drainage can be divided into two distinct approaches, namely, gastrohepatic (or EUS-guided hepaticogastrostomy) and extrahepatic (or EUS-guided choledocoduodenostomy) approaches (Figure 3). Each approach can be divided into direct drainage and the Rendez-vous technique. The latter has been preferred by some for benign diseases, but it is important to note that it is technically challenging, with a higher risk of failure and complications. We consider this technique to be discouraged. When the duodenum is accessible, choledocoduodenostomy can be attempted, and the development of lumen-appossable metallic stents (LAMSs) has simplified this approach. Recently, EUS BD has been evaluated as a first-line treatment instead of ERCP for malignant biliary obstruction, mainly due to the high technical success rate and the absence of papilla manipulation, which can decrease the risk of pancreatitis. A recent meta-analysis evaluated EUS BD as the primary palliation option for distal biliary obstruction, describing equivalent technical and clinical success, with no difference in adverse events between EUS BD and ERCP [76]. Further high-quality multicenter and controlled studies are clearly needed to determine the right place for EUS-guided BD techniques beyond ERCP failures. Choledocoduodenostomy, equivalent to side-to side biliodigestive anastomosis, is prone to alimentary biliary reflux, causing cholangitis, and may thus be preferred for short-term drainage. For a nonaccessible duodenum, the gastrohepatic approach with hepatogastrostomy is the best approach, which can also be considered in benign conditions and in cases of biliodigestive anastomosis dysfunction after Whipple

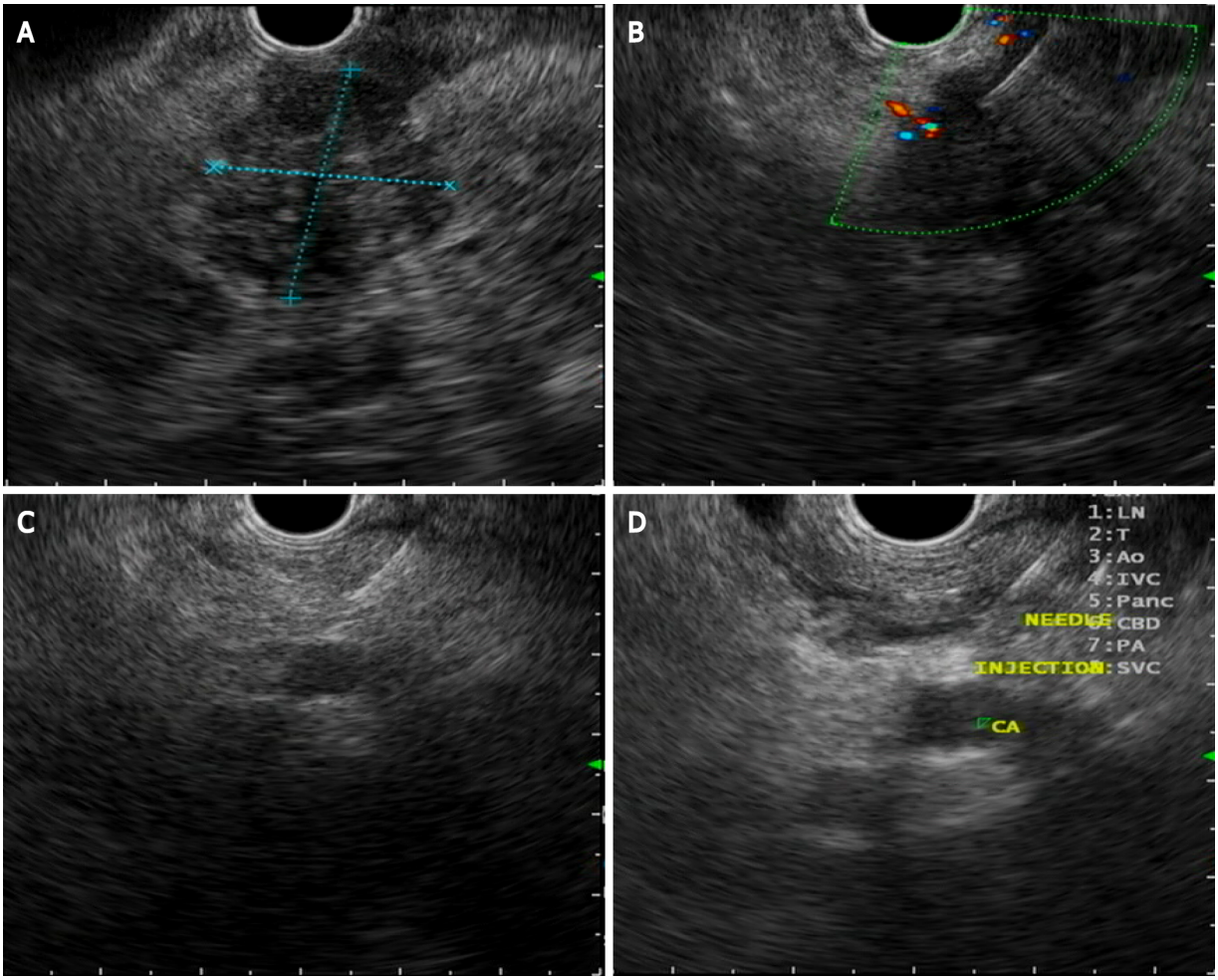

Figure 2 Celiac plexus neurolysis. A: Pancreatic ductal adenocarcinoma located in the head of the pancreas; B: Endoscopic ultrasound (EUS)-guided tissue acquisition with a fine needle aspiration needle; C: EUS-guided puncture of the celiac plexus area; D: EUS-guided neurolysis with absolute alcohol injection.

resection. A dilated left intrahepatic duct is needed to succeed in this route. A partially covered metallic stent (uncovered intrahepatic portion) has been developed for this approach, with promising results. A systematic review that evaluated the efficacy and safety of EUS BD found no difference in technical success and adverse event rates between transgastric and transduodenal approaches[77].

Even though LAMSs are highly useful for the EUS BD approach, they are a regionally limited device. Regarding the risk of recurrent biliary obstruction, EUS BD has a lower risk of tumor ingrowth but a higher risk of food impaction than ERCP BD. Stent patency for EUS BD is comparable to ERCP BD. A study by Park *et al*[78] described a cumulative stent patency of 379 d for EUS BD[78].

EUS-guided gastroenterostomy

Gastric outlet obstruction (GOO) is present in 15%-25% of patients with PDAC[79] and has a severe impact on quality of life. Traditionally, this complication is treated either surgically or with self-expandable metallic stents (SEMSs) placed by the endoscopic route. Recently, EUS-guided gastroenterostomy has emerged as a successful alternative for GOO management[80]. To achieve this goal, LAMSs are used to create a communication between the stomach and the small bowel distal to the obstruction. A recent meta-analysis described a technical success rate of 92% and clinical success rate of 90%, with a pooled incidence of adverse events of 12%[81].

Another application of interventional EUS is for the treatment of afferent limb syndrome (ALS). This is a rare late postsurgical complication of PDAC pancreaticoduodenectomy, most frequently due to local cancer recurrence and mechanical obstruction, with dilation of the afferent limb and accumulation of biliopancreatic fluid. EUS-guided drainage with a LAMS has been described, which provides an adequate therapeutic approach to decompress the limb for palliative and symptomatic treatment[82]. Most of the evidence for these two EUS therapeutic applications is

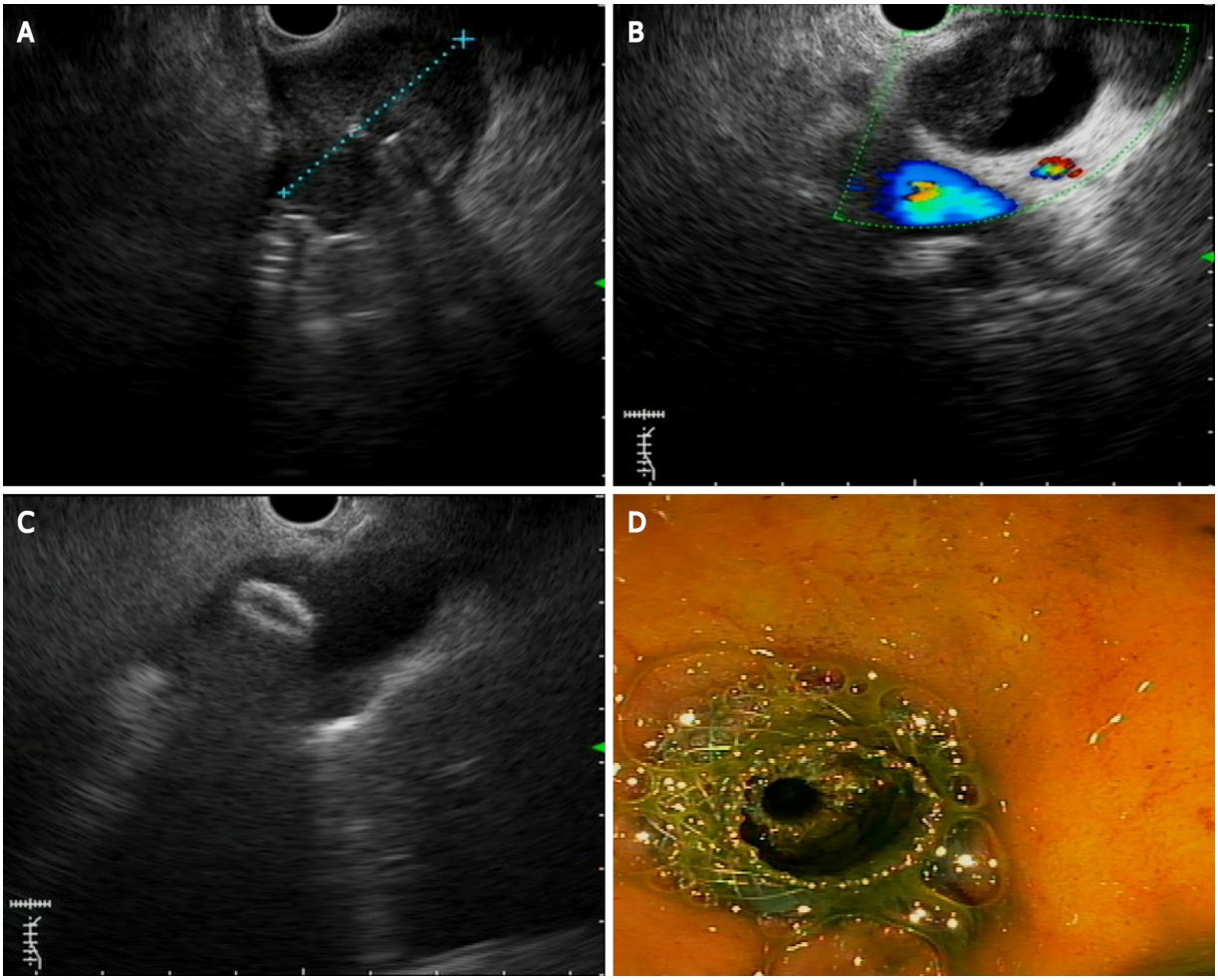

Figure 3 Endoscopic ultrasound-guided choledocoduodenostomy. A: Pancreatic ductal adenocarcinoma (PDAC) located in the pancreatic head; B: Common bile duct dilation caused by PDAC; C: Lumen-appossable metallic stents (LAMS) distal flange opening inside the bile duct; D: Biliary drainage after LAMS placement.

primarily retrospective. Even though they seem to be promising techniques, well-designed multicentric, prospective, controlled trials are needed to validate these resources.

CONCLUSION

Since its introduction as an endoscopic technique, EUS has evolved from a diagnostic imaging device toward a therapeutic tool, primarily for palliative cancer management. Considerable progress has been made, particularly in the diagnosis and management of PDAC. New imaging techniques can improve the differential diagnosis of focal pancreatic lesions and can decrease the bias of human imaging interpretation. EUS is the standard method for tissue acquisition, and the development of new "cutting" needles allows the procurement of core tissue for molecular profiling and personalized oncological treatment. Outstanding progress has been made in EUS interventional procedures, mainly for biliary drainage and local tumor ablation, with good technical and clinical success and fewer complications compared to other techniques. Future randomized controlled trials should be directed to evaluate the role of EUS-guided treatment, such as RFA, for unresectable pancreatic cancer or patients unsuitable for surgery. Diagnostic and interventional EUS have become essential in the workup and management of PDAC.

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ORIGINAL ARTICLE

Retrospective Study

Feasibility of gastric endoscopic submucosal dissection in elderly patients aged ≥ 80 years

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Abstract

BACKGROUND

Endoscopic resection, especially endoscopic submucosal dissection (ESD), is increasingly performed in elderly patients with early gastric cancer, and lesions beyond the expanded indications are also resected endoscopically in some patients. It is essential to assess whether gastric ESD is safe and suitable for elderly patients and investigate what type of lesions carry an increased risk of ESD-related complications.

AIM

To assess the efficacy and feasibility of gastric ESD for elderly patients, and define high-risk lesions and prognostic indicators.

METHODS

Among a total of 1169 sessions of gastric ESD performed in Kanagawa Cancer Center Hospital from 2006 to 2014, 179 sessions (15.3%) were performed in patients aged ≥ 80 years, and 172 of these sessions were done in patients with a final diagnosis of gastric cancer. These patients were studied retrospectively to

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Institutional review board statement: This study has been approved by the research ethics committee of Kanagawa Cancer Center, which complies with International Guidelines for Ethical Review of Epidemiological Studies.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. According to "Ethical Guidelines for Medical and Health Research Involving Human Subjects" published by Japanese Ministry of Health, Labor and Welfare, opt-out is accepted for practical procedure to obtain informed consent from the recruited patients, in retrospective study without any invasion or newly investigated information after recruitment. For our study, we have put information concerning the study on Kanagawa Cancer Center HP, to give recruited patients a chance to refuse entry to the study.

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evaluate short-term outcomes and survival. The short-term outcomes included the rates of *en bloc* resection and curative resection, complications, and procedure-related mortality. Curability was assessed according to the Japanese Gastric Cancer Treatment Guidelines 2010. Fisher's exact test was used to statistically analyze risk factors. Clinical characteristics of each group were compared using Fisher's exact test and Mann-Whitney *U* test. Survival rates at each time point were based on Kaplan-Meier estimation. Overall survival rates were compared between patients with gastric cancer in each group with use of the log-rank test. To identify prognostic factors that jointly predict the hazard of death while controlling for model overfitting, we used the least absolute shrinkage and selection operator (LASSO) Cox regression model including factors curative/noncurative, age, gender, body mass index, prognostic nutritional index, Charlson comorbidity index (CCI), Glasgow prognostic score, neutrophil-to-lymphocyte ratio, and antithrombotic agent use. We selected the LASSO Cox regression model that resulted in minimal prediction error in 10-fold cross-validation. $P < 0.05$ was considered statistically significant.

RESULTS

The *en bloc* dissection rate was 97.1%, indicating that a high quality of treatment was achieved even in elderly patients. As for complications, the rates of bleeding, perforation and aspiration pneumonitis were 3.4%, 1.1% and 0.6%, respectively. These complication rates indicated that ESD was not associated with a particularly higher risk in elderly patients than in nonelderly patients. A dissection incision > 40 mm, lesions associated with depressions, and lesions with ulcers were risk factors for post-ESD bleeding, and location of the lesion in the upper third of the stomach was a risk factor for perforation in elderly patients ($P < 0.05$). Location of the lesion in the lower third of the stomach tended to be associated with a higher risk of bleeding. The overall survival (OS) did not differ significantly between curative and noncurative ESD ($P = 0.69$). In patients without additional surgery, OS rate was significantly lower in patients with a high CCI (≥ 2) than in those with a low CCI (≤ 1) ($P < 0.001$).

CONCLUSION

Gastric ESD is feasible even in patients aged ≥ 80 years. Observation without additional surgery after noncurative ESD is reasonable, especially in elderly patients with CCI ≥ 2.

Key Words: Endoscopic submucosal dissection; Elderly; Charlson comorbidity index; Early gastric cancer; Complications; Prognostic indicators

Core Tip: This was a retrospective study to evaluate the efficacy and feasibility of gastric endoscopic submucosal dissection in elderly patients aged ≥ 80 years. The rates of *en bloc* dissection, bleeding, perforation and aspiration pneumonitis were 97.1%, 3.4%, 1.1% and 0.6%, respectively. These rates are similar to the rates in nonelderly patients reported previously. Risk factors for bleeding were incision > 40 mm, lesions associated with depressions, and ulcerative lesions. A risk factor for perforation was location in the upper third of the stomach. Charlson comorbidity index ≥ 2 was an indicator of poor prognosis regardless of curability.

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INTRODUCTION

Early gastric cancer (EGC) is defined as gastric cancer confined to the mucosa and submucosa[1]. Increasing numbers of EGCs are being detected in Japan[2,3], and EGCs currently account for > 60% of all detected cases of gastric cancer[4]. Since the development of endoscopic submucosal dissection (ESD), the treatment of EGC has changed dramatically[5,6]. Various techniques have considerably reduced the technical limitations of endoscopic resection (ER), and EGCs can now be freely resected, independently of size and shape[6-8]. Many EGCs that would have been surgically resected previously are now resected endoscopically. The most attractive point of ESD as compared with open surgery is its lower invasiveness and the ability to avoid deterioration in the quality of life.

The elderly population is increasing rapidly in Japan. The average life span is 80.50 years for men and 86.83 years for women, according to statistics reported by the Ministry of Health, Labour and Welfare, Japan in 2014. Surgery carries an increased risk in elderly patients because of poor physical status or serious underlying diseases [9,10]. Thus ER, especially ESD, is being increasingly performed in elderly patients[10-14]. Because this trend is expected to continue, it is necessary to assess whether ESD is actually safe and suitable for elderly patients. In addition, more clearly defining high-risk lesions associated is prerequisite to safe treatment.

MATERIALS AND METHODS

Patients

A total of 1169 sessions of ESD were performed to treat gastric diseases (mainly EGCs and gastric adenomas, as well as some non-neoplastic lesions) in Kanagawa Cancer Center Hospital between January 2006 and December 2014, and 179 (15.3%) of these sessions were performed in a total of 131 patients who were aged ≥ 80 years. Among the resected specimens, gastric cancers were finally diagnosed in 175 lesions treated by 172 sessions of ESD in 124 patients. These cases were studied retrospectively.

ESD procedure

Around-the-lesion biopsy was performed beforehand to confirm the margin of the lesions, if necessary. On the day of ESD, the margin was identified again using white light endoscopy, chromoendoscopy with indigo carmine solution, and narrow-band imaging. All-around-the-lesion marking was carried out with the use of small multiple cautery units. Submucosal injection was performed to lift the mucosal layer. Glyceol (10% glycerol and 5% fructose; Chugai Pharmaceutical Co., Tokyo, Japan) or MucoUp (0.4% sodium hyaluronate; Johnson & Johnson, New Brunswick, NJ, United States) with a small amount of indigo carmine was used as the injection solution. A circumferential mucosal incision and submucosal dissection were performed using a needle knife (Olympus Optical Co. Ltd., Tokyo, Japan). The high-frequency generators used were ICC200 or VIO300D (ERBE Elektromedizin GmbH, Tübingen, Germany).

Short-term outcomes

The short-term outcomes included the rates of *en bloc* resection and curative resection, complications, and procedure-related mortality. Curability was assessed according to the Japanese Gastric Cancer Treatment Guidelines 2010[15]. A curative resection was defined as satisfying all the following conditions: *en bloc* resection, negative horizontal and vertical margin, no lymphovascular infiltration, and absolute or expanded indication for ER. Differentiated type intramucosal cancer ≤ 20 mm in size without ulceration was categorized as a lesion of absolute indication. A lesion of expanded indications was as follows: Differentiated type intramucosal cancer > 20 mm in size without ulceration; differentiated type intramucosal cancer ≤ 30 mm in size with ulceration; differentiated type submucosal superficial cancer ≤ 30 mm in size; and undifferentiated type intramucosal cancer ≤ 20 mm in size without ulceration.

As for complications, bleeding, perforation and aspiration pneumonitis were assessed. Bleeding was defined as the occurrence of melena or hematemesis; detection of ongoing hemorrhage; or the presence of coagulated blood in the stomach with apparent bleeding spots on endoscopic examination, which was basically performed routinely in all patients on the next day of ESD. Perforation was confirmed by observation of mesenteric fat during ESD or by detection of free air on X-ray films. Aspiration pneumonitis was diagnosed on the basis of clinical findings and X-ray films. Procedure-related mortality was defined as death within 30 d due to complic-

ations. In patients who had complications, patient-related factors, such as World Health Organization performance status and underlying disease, as well as lesion-related factors, such as location, size, and macroscopic aspects were investigated.

Long-term outcomes

For evaluation of long-term outcomes, a patient who had experienced noncurative ESD within the last 5 years (n = 1) and patients who underwent additional surgery after ESD (n = 3) were excluded from the target of analysis. Overall survival (OS) was evaluated starting from the date of ESD to the date of death or the last verified date of survival. To determine the prognostic indicators for elderly patients with EGC treated by ESD, we also evaluated the clinical characteristics of the patients who did not undergo additional surgery after ESD (n = 120), using age, gender, body mass index (BMI), prognostic nutritional index (PNI), Charlson comorbidity index (CCI), Glasgow prognostic score (GPS), neutrophil-to-lymphocyte ratio (NLR), and use of antithrombotic agents.

Statistical analysis

To estimate affecting factors related to complications, relative risks were calculated. Fisher's exact test was used to statistically analyze risk factors. Clinical characteristics of each group were compared using Fisher's exact test and Mann-Whitney U test. Survival rates at each time point were based on Kaplan-Meier estimation. OS rates were compared with the log-rank test between patients with gastric cancer in each group. To identify prognostic factors that jointly predict the hazard of death while controlling for model overfitting, the least absolute shrinkage and selection operator (LASSO) Cox regression model including factors curative/noncurative, age, gender, BMI, PNI, CCI, GPS, NLR and antithrombotic agent use was used (R package glmnet) [16]. We selected the LASSO Cox regression model that resulted in minimal prediction error in 10-fold cross-validation. $P < 0.05$ was considered statistically significant.

All statistical analyses were conducted using the EZR software, version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan)[17] and R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). The statistical review of the study was performed by a biomedical statistician.

RESULTS

Short-term outcomes

Short-term outcomes are shown in Table 1. Within 172 sessions of ESD, two different specimens of multiple lesions were resected at the same time in three sessions; only one specimen was resected for each treatment in 168 sessions; and one lesion was unresectable in one session. A total of 174 specimens were thus resected from 175 lesions in 172 sessions of ESD. The *en bloc* dissection rate and the curative dissection rate were 97.1% and 77.1%, respectively. Six lesions (3.4%) had postoperative bleeding, two (1.1%) had intraoperative perforation, and one patient (0.6%) had aspiration pneumonitis after ESD. Blood transfusion was required in one patient. There were no procedure-related deaths.

The characteristics of the treated lesions and patients are shown in Table 2. Macroscopically, flat-type shaped lesions (85.7%) predominated over protruded-type lesions (13.7%). There was one advanced type 1 lesion, which was misdiagnosed as EGC type 0-I before treatment. Of 124 recruited patients, 38 (30.6%) had circulatory underlying diseases, nine (7.3%) had respiratory underlying diseases, and 22.6% of the patients were receiving at least one antithrombotic agent.

In the present study of elderly patients, lesions that did not meet the indication criteria were also treated. The details of noncurative lesions and noncurative factors are shown in Table 3. Among 40 noncurative lesions, 32 (80.0%) were differentiated type, and eight (20.0%) were undifferentiated type. The noncurative factors were depth of invasion in 30.0%, oversize in 20.0%, positive ulceration associated with undifferentiated components in 12.5%, and positive or uncertain lymph vascular invasion in 35.0% of the noncurative lesions.

The patients with complications are summarized in Table 4. One patient had both postoperative bleeding and aspiration pneumonitis, and the others had one complication each. None of patients with postoperative bleeding was receiving any antithrombotic agents.

Table 1 Short-term outcomes of ESD, *n* (%)

Location of the lesions (n = 175)[1]	
Upper third	33 (18.9)
Middle third	57 (32.6)
Lower third	85 (48.6)
Size of dissected specimen (n = 174)[2]	
Range	9-110 mm
Median	30 mm
Average	33.4 mm
ESD quality (n = 175)[2]	
En bloc dissection	170 (97.1)
Fractional dissection	4 (2.3)
Not dissected endoscopically	1 (0.6)
Curability (n = 175)[1]	
Curative dissection	135 (77.1)
Non-curative dissection	40 (22.9)
Complications	
ESD sessions (n = 172) with any complication	8 (4.7)
Bleeding (n = 175)[1]	6 (3.4)
Perforation (n = 175)[1]	2 (1.1)
Aspiration pneumonitis (n = 172)[3]	1 (0.6)
Procedure-related death (n = 172)[3]	0

[1]Location, Endoscopic submucosal dissection (ESD) quality (*en bloc* or fractional dissection rate), curability (curative or noncurative dissection rate), and complications of bleeding and perforation calculated with respect to the total number of 175 treated lesions.
[2]Size of dissected specimen measured only in endoscopically resected cases (n = 174).
[3]Number of ESD sessions (total n = 172) associated with aspiration pneumonitis. ESD: Endoscopic submucosal dissection.

The relation of complications to lesion location and size of resected specimen is summarized in Table 5. Lesion location in the lower third of the stomach and a resected specimen size > 40 mm tended to have higher bleeding rates. Lesion location in the upper third of the stomach and a resected specimen size > 40 mm tended to be associated with higher perforation rates.

The relative risks of lesion location and resected specimen size are shown in Table 6. Resected specimens > 40 mm, macroscopic shape with depressive component, and presence of ulceration were determined to be risk factors for bleeding ($P < 0.05$). Location of the lesion in the upper third of the stomach was determined to be a risk factor for perforation ($P < 0.05$).

Long-term outcomes

Survival curves according to the curability are shown in Figure 1. The patients were divided into two groups: Those who underwent only curative ESD (curative ESD group, n = 87), and those who underwent noncurative ESD without additional surgery (noncurative ESD group, n = 33). Patients who had undergone dissection more than once were classified as noncurative when ESD was noncurative at least once. A total of 32 patients (26.7%) died during a median follow-up period of 2005 d (range, 83-4774 d). Twenty-four of the patients who died were in the curative ESD group and eight were in the noncurative ESD group. The cause of death was gastric cancer in none of them. The OS rate did not differ significantly between the curative and the non-curative ESD groups (P = 0.69).

Prognostic factors for OS using LASSO in the patients who did not undergo additional surgery (n = 120) are shown in Table 7. Among these clinical characteristics, gender and CCI, one of most widely used and validated comorbidity scoring system to

Table 2 Characteristics of treated lesions and patients, *n* (%)

(A) Lesions (*n* = 175)	
Macroscopic type	
Protruded type (0-I, 0-I+IIa, 0-I+IIb, 0-I+IIc)	24 (13.7)
Flat type (0-IIa, 0-IIa+IIc, 0-IIb, 0-IIc, 0-IIc+IIa)	150 (85.7)
Advanced (type 1)	1 (0.6)
Ulceration	
UL (+)	22 (12.6)
UL ()	153 (87.4)
Depth of invasion	
M	152 (86.9)
≥ SM	23 (13.1)
(B) Patients (*n* = 124)	
Underlying disease	
Circulatory	38 (30.6)
Respiratory	9 (7.3)
Renal	0
Antithrombotic agent	
Taking	28 (22.6)

UL: Ulceration; M: Mucosa; SM: Submucosa.

measure comorbidity status, were significantly associated with OS. As median CCI in each group was 1, patients were divided in two groups according to CCI ≤ 1 or > 1. The survival curve of patients with low CCI ≤ 1 (*n* = 100) and those with high CCI ≥ 2 (*n* = 20) are shown in Figure 2. The OS rate was significantly different between the two groups ($P < 0.001$).

DISCUSSION

In Japan, the morbidity rate of gastric cancer has been rapidly decreasing according to the Center for Cancer Control and Information Services, National Cancer Center, Japan. Nonetheless, the number of EGCs treated endoscopically has dramatically increased. The increased use of ER seems to be attributed to three reasons. The first reason is the expansion of the indications for ER. Because ER is a local resection procedure without lymphadenectomy, the indications for ER are limited to conditions expected to have no lymph node metastasis[15]. Previous studies of patients who underwent surgery for gastric cancer have evaluated conditions associated with no lymph node metastasis. The second reason is progress in endoscopic techniques[6-8]. The final reason is the minimal invasiveness of ESD. ESD is far less invasive than open surgery, and can prevent symptoms associated with a small capacity of stomach after surgery.

Although minimal invasiveness is undoubtedly attractive for elderly patients because they have higher incidences of underlying diseases than younger patients have and are sometimes in poor general condition[9,10], the feasibility of ESD remains to be fully evaluated. In our study, complications occurred only in 4.7% of patients, without any procedure-related deaths. In previous studies of elderly patients, the rate of bleeding ranged from 2.5% to 9.6%[10-14], except for the study by Hirasaki *et al*[10], which reported a bleeding rate of 43.4%[3], and the rates of perforation and of pneumonia ranged from 1.5% to 5.0% and 0.5% to 2.2%, respectively. In most of these studies, ESD was not associated with particularly higher risk in elderly than in nonelderly patients. Indeed, the rates of bleeding and perforation among patients of all ages were reported to range from 3.7% to 15.6% and 1.2% to 6.7%, respectively[18-22].

Table 3 Details of noncurative lesions, and estimated noncurative factors of 40 noncurative lesions

(A) Details of noncurative lesions (*n* = 40)

	Depth of invasion			
	M	SM1	SM2	≥ MP
Histological type				
Differentiated (tub1, tub2, pap)	19	4	8	1
Undifferentiated (por, sig, muc)	4	2	2	0

(B) Estimated non-curative factors of 40 non-curative lesions, *n* (%)

Depth of invasion	
≥ SM2, differentiated	8 (20)
≥ SM, undifferentiated	4 (10)
Lesion size	
≥ 30 mm, differentiated, UL (+)	2 (5)
≥ 30 mm, differentiated, SM1	1 (2.5)
≥ 20 mm, undifferentiated	5 (12.5)
Ulceration	
UL (+) with undifferentiated components	5 (12.5)
Lymphovascular invasion	
Ly +/uncertain	7 (17.5)
V +/uncertain	7 (17.5)
Surgical margin	
Positive	7 (17.5)
Uncertain	21 (52.5)
Not dissected endoscopically	1 (2.5)

M: Mucosa; SM: Submucosa; MP: Muscularis propria; UL: Ulceration; Ly: Lymphatic invasion; V: Venous invasion.

In nonelderly patients, Lin *et al*[23] reported that the rates of bleeding, perforation and procedure-related pneumonia were 2.9%, 1.1% and 0.4%, respectively, in their meta-analysis of nine previous studies of gastric ESD. These previous reports and present study suggest that the rates of complications of ESD in elderly patients are not particularly higher than the rates in nonelderly or patients of all ages. Accordingly, we argue that gastric ESD is feasible even in elderly patients aged ≥ 80 years.

However, some studies have reported that ESD carries a higher risk in elderly patients than in younger patients[13,21]. Toyokawa *et al*[13] reported that the bleeding rate was significantly higher in the elderly group (age ≥ 75 years) than in the nonelderly group (age < 75 years). However, in multivariate analysis, high age was not in itself an independent predictor of bleeding, and the reason why the bleeding rate was higher in the elderly group was unclear. It was also reported by Toyokawa *et al*[21] in another report that age ≥ 80 years was associated with a significantly higher risk of delayed bleeding after ESD, and they concluded that the use of antiplatelet agents or anticoagulants was not the reason for delayed bleeding in elderly patients. Also in that study, they could not specify the reason why delayed bleeding was predominant in elderly patients over nonelderly patients. In our institution, endoscopic examination on the next day of ESD was routinely performed, and coagulation of visible vessels at the ulcer floor was carried out. This endoscopic examination may have contributed to low incidence of bleeding in our present study. In any case, attentive precautionary endoscopic hemostasis after dissection is crucial for aged patients, as they demonstrate age-related physiological decline with higher incidence of underlying diseases and worse overall condition[13].

Even if gastric ESD is feasible in elderly patients, complications can have severe consequences. To acknowledge the characteristics of lesions associated with higher

Table 4 Details of patients who had complications of endoscopic submucosal dissection

Age (yr)	Gender	Ps	Underlying disease	Past history	Location[1]	Size (mm)	Macroscopic type	Final pathology	Curability	Specimen (mm)	Complications
83	F	1		Post-BHA	L, Ant	40	0-IIc, UL (+)	Tub2 > por2, M, ly0, v0, HM0, VM0	Noncurative	60	Bleeding G2
83	M	0			L, Ant	10	0-IIc, UL (+)	Tub1 > tub2, M, ly0, v0, HM0, VM0	Curative	20	Bleeding G2
92	M	0		Laryngeal cancer	U, Post	50	Type1	Surgical resection: pap > tub, SS, ly0, v1, NX, HMX	Noncurative	52[2]	Perforation G3
89	M	3		Brain cancer	M, Les	33	0-IIc, UL (+)	Sig/por2, M, ly0, v0, HM0, VM0	Noncurative	68	Bleeding G3, pneumonitis G2
83	F	2	AD, Depression		U, Les	15	0-IIa	Tub1, M, ly0, v0, HM0, VM0	Curative	30	Perforation G2
82	F	0			(1) L, Ant	(1) 20	(1) 0-IIc	(1) Tub2 > tub1 > por, M, ly0, v0, HM0, VM0	(1) Curative	54	Bleeding G2
					(2) L, Ant	(2)10	(2)0-IIc	(2) Tub1-tub2, M, ly0, v0, HM0, VM0	(2) Curative		
84	M	2	AP, COPD		L, Les	15	0-IIc	Por1, M, ly0, v0, HMX, VMX	Noncurative	40	Bleeding G2
80	M	0		Colon cancer, EGC	L, Les	16	0-IIa+IIc, UL (+)	Tub1 > tub2 > por, M, ly0, v0, HM0, VM0	Curative	47	Bleeding G2

[1]Location divided into three regions of the stomach; U (upper third), M (middle third), and L (lower third), respectively.
[2]Size of all-around incision of endoscopic submucosal dissection measured in a surgically resected specimen.
PS: Performance status; BHA: Bipolar hip arthroplasty; AD: Alzheimer disease; UL: Ulceration; AP: Angina pectoris; COPD: Chronic obstructive pulmonary disease; EGC: Early gastric cancer; M: Mucosa; SM: Submucosa; SS: Subserosa; ly: Lymphatic invasion; v: Venous invasion; HM: Horizontal margin; VM: Vertical margin; N: Lymph node metastasis; L: Lower third; M: Middle third; U: Upper third.

risks in elderly patients is essential to a safe procedure. Kim *et al*[22] reported that the risk of perforation associated with ESD is higher for lesions located in the gastric body than those located in the antrum. Toyokawa *et al*[21] reported that ESD carried a high risk of perforation when EGCs located in the upper third of the stomach were dissected. Our results that lesion location in the upper third of the stomach was a significant risk factor, and lesion size > 40 mm tended toward a higher risk of perforation in elderly patients seem to be consistent with previous studies performed in patients of all ages.

As for bleeding, Chung *et al*[18] reported that the risk of delayed bleeding after ESD was significantly higher for lesions located in the upper portion of the stomach. In contrast, in our study focusing on elderly patients, lesions located in the lower portion of the stomach tended to have a higher risk of bleeding. As for macroscopic shape, lesions with depressive components such as 0-IIc, 0-IIa + IIc, 0-IIc + IIa, and 0-I + IIc and lesions with ulceration were associated with bleeding after ESD. In contrast, treatment with antithrombotic agents was not associated with bleeding. We speculate that strong peristaltic contractions of the gastric antrum increased the risk of bleeding in the lower portion of the stomach. In addition, a resected lesion size > 40 mm in diameter was determined to be a risk factor for bleeding. Moreover, the median lesion size in patients with bleeding was 50.5 mm (range, 20-68 mm), which was about 70% larger than median lesion size of 30 mm (range, 9-110 mm) in the study group as a whole. We therefore recommend meticulous preventive endoscopic hemostasis after resecting lesions > 40 mm, especially those located in the lower third of the stomach, and lesions with depressive aspects or ulceration, when treating elderly patients.

Table 5 Relations of complications to location or dissected size of endoscopic submucosal dissection specimens, *n* (%)

	Bleeding (+)	Bleeding (-)	Perforation (+)	Perforation (-)	Total
	n = 6	*n* = 169	*n* = 2	*n* = 173	*n* = 175
Location					
Upper third	0	33 (100)	2 (6.1)	31 (93.9)	33
Middle third	1 (1.6)	56 (98.4)	0	57 (100)	57
Lower third	5 (5.9)	80 (94.1)	0	85 (100)	85
Size of specimen					
≤ 20 mm	1 (3.3)	29 (96.7)	0	30 (100)	30
21-40 mm	1 (1.0)	102 (99.0)	1 (1.0)	102 (99.0)	103
41-60 mm	3 (8.1)	34 (91.9)	1 (2.7)[1]	36 (97.3)	37
≥ 61 mm	1 (20.0)	4 (80.0)	0	5 (100)	5

[1]Not endoscopically dissected case.
Size of all-around incision of endoscopic submucosal dissection measured in a surgically resected specimen.

To prevent aspiration during ESD, an overtube was inserted in all patients. Accordingly, the rate of aspiration pneumonitis was as low as 0.6%. In contrast, Isomoto *et al*[12] reported that aspiration pneumonitis occurred in 2.2% of patients aged ≥ 75 years, which was more frequent than in younger patients. In contrast, Lee *et al*[24] reported that the risk of aspiration might be increased by endoscopic procedures with a longer duration.

In the present study of elderly patients, lesions that did not meet the indication criteria were also treated. Accordingly, the curative dissection rate of ESD was only 77.1%. Abe *et al*[14] reported that the curative rate of ESD was 77.9% in their multicenter study of ESD in patients aged ≥ 80 years, consistent with our results. The question arises whether dissecting lesions beyond expanded indications was meaningless? Kang *et al*[25] recently reported that even if the lesions are beyond expanded indications, ESD reduces the risk of death from gastric cancer, although it does not completely cure the disease in some patients. In our study, the disease-specific 5-year survival rate and 5-year OS rate in the noncurative ESD group were as high as 100% and 76.9%, respectively. These rates were higher than 5-year survival rate of patients with EGC who did not undergo resection (62.8%) as reported by Tsukuma *et al*[26]. Furthermore, the OS of the noncurative ESD group was equivalent to that of the curative ESD group. Although the number of patients in our study was small, and our results may have been influenced by selection bias, our findings suggest that ESD might be effective for EGC beyond expanded indications. Indeed, although 32 of 120 recruited patients died during the follow-up period, none of them died of gastric cancer. The causes of death in the other patients were malignancy in other organs in seven patients, respiratory diseases in five patients, and uncertain in 20 patients.

Tsukuma *et al*[26] reported that the median interval required for EGC to progress to an advanced stage was 44 mo. Moreover, older patients tended to have shorter intervals to the development of advanced disease, and it was 36 mo in patients aged > 75 years[27]. We thus consider it reasonable to endoscopically resect lesions beyond expanded indications if surgery is unacceptable, with the goal of preventing symptoms that may develop in the future, in patients who are expected to survival for longer than 36 mo.

In this study, local recurrence developed in only one (3.0%) of 33 patients in the noncurative ESD group. Similarly, Abe *et al*[14] reported that local recurrence developed in 3.3% and distant metastasis developed in 5.5% of patients who did not undergo additional surgery after noncurative ESD. Kusano *et al*[28] reported that survival was improved by additional surgery following noncurative ER in elderly patients. In contrast, Ahn *et al*[29] reported that the mortality rate was significantly higher in the presence of lymphovascular invasion than in the absence of such invasion in patients with differentiated EGC who underwent nonsurgical follow-up after noncurative ER. Thus, if possible, additional surgery is advisable after noncurative ESD, even in elderly patients, especially when lymphovascular invasion is

Table 6 Relative risks of location and size for bleeding or perforation

(A) Relative risk of location lower third, size > 40 mm, macroscopic shape, presence or absence of ulceration, and depth of invasion for bleeding			
	Bleeding (+)	**Relative risk**	***P* value**
Location			
Lower third	5.9% (5/85)	5.3	0.11
Upper third, middle third	1.1% (1/90)		
Dissected size			
≥ 41 mm	9.5% (4/42)	6.3	0.030
≤ 40 mm	1.5% (2/133)		
Macroscopic shape			
Depressive component (+)	8.2% (6/73)		0.005
Depressive component ()	0% (0/102)		
Ulceration			
UL (+)	18.2% (4/22)	13.9	0.003
UL ()	1.3% (2/153)		
Depth of invasion			
≥ SM	3.9% (6/152)		1
M	0% (0/23)		
(B) Relative risk of location upper third, size > 40 mm, macroscopic shape, presence or absence of ulceration, and depth of invasion for perforation			
	Perforation (+)	**Relative risk**	***P* value**
Location			
Upper third	6.3% (2/32)		0.033
Middle third, lower third	0% (1/143)		
Dissected size			
≥ 41 mm	2.4% (1/42)	3.2	0.423
≤ 40 mm	0.8% (1/133)		
Macroscopic shape			
Depressive component (+)	0% (0/73)	-	0.511
Depressive component ()	2.0% (2/102)		
Ulceration			
UL (+)	0% (0/22)	-	1
UL ()	1.3% (2/153)		
Depth of invasion			
≥ SM	0.7% (1/152)	6.6	0.246
M	4.3% (1/23)		

UL: Ulceration; M: Mucosa; SM: Submucosa.

confirmed histologically.

CCI was developed to assess the risk of death from comorbidities and has been widely used to evaluate clinical outcomes, such as prognosis or complications. CCI was calculated as the sum of the scores assigned to several comorbidities (myocardial infarction, congestive heart failure, cerebrovascular disease, uncomplicated diabetes, moderate-to-severe chronic kidney disease, moderate-to-severe liver disease, solid tumor, leukemia *etc.*) based on the original definition[30]. In our study, curability of ESD was not associated with OS rate. CCI was indicated to be the only factor

Table 7 Prognostic factors for overall survival (*n* = 120)

	Cox LASSO
Curability	
Noncurative	–
Patient	–
Age	–
Gender: Male	0.416
BMI	–
PNI	–
CCI > 1	0.477
GPS	–
NLR	–
Antithrombotic agent (+)	–

LASSO: Least absolute shrinkage and selection operator; BMI: Body mass index; PNI: Prognostic nutritional index; CCI: Charlson comorbidity index; GPS: Glasgow prognostic score; NLR: neutrophil-to-lymphocyte ratio.

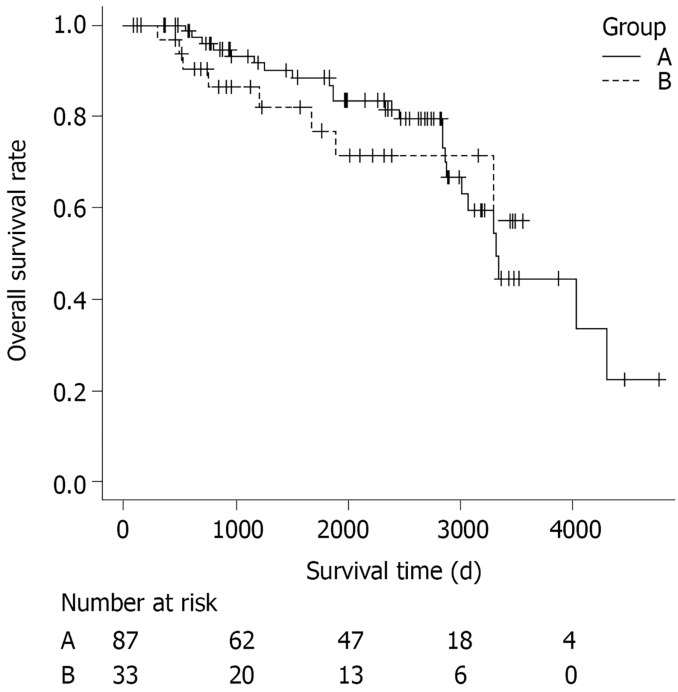

Figure 1 Overall survival of curative and noncurative patients. Group A: Curative endoscopic submucosal dissection (ESD) group (*n* = 87); Group B: Noncurative ESD group (*n* = 33). A total of 32 patients (26.7%) died during a median follow-up of 2005 d (range, 83-4774 d). Twenty-four of the patients who died were in the curative ESD group and eight were in the noncurative ESD group. The cause of death was gastric cancer in none of them. The overall survival rate did not differ significantly between the curative and noncurative ESD groups (*P* = 0.69).

associated with prognosis, among various clinical characteristics such as BMI, PNI, GPS and NLR. However, Iwai *et al*[31] reported that CCI ≥ 3 and PNI < 47.7 were both significantly associated with lower OS rate. Whether nutritional status is truly a predictor of long-term prognosis is controversial. According to our results, we suggest that observation without additional surgery after noncurative ESD may be considered, especially in elderly patients with CCI > 1.

The limitation of our study was that it was retrospective. Although complications are expected to differ depending on concomitant diseases, we cannot confirm the patients' characteristics in detail. Moreover, we had only a few cases of bleeding and perforation, as this was a single-center study with a limited number of recruited

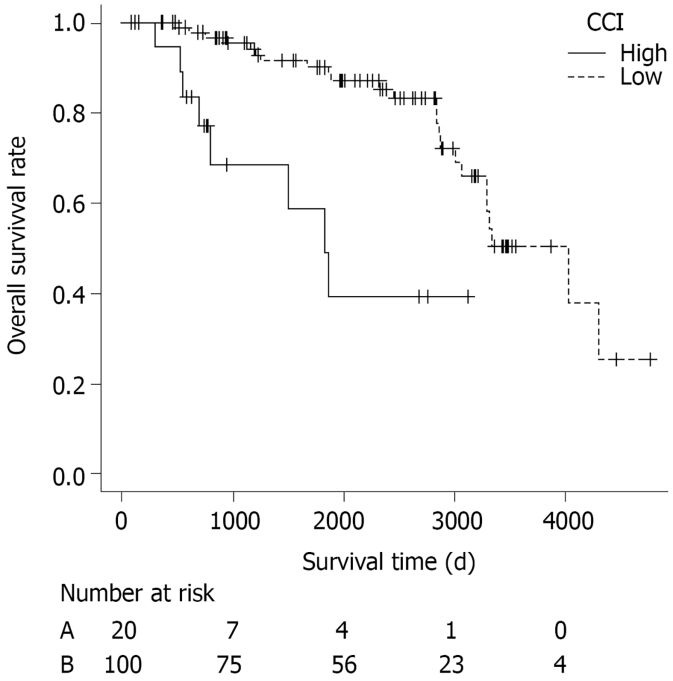

Figure 2 Overall survival of patients with high and low Charlson comorbidity index. Charlson comorbidity index (CCI) High: Patients with CCI ≥ 2 (*n* = 20); CCI Low: Patients with CCI ≤ 1 (*n* = 100). Overall survival rate was significantly different between the two groups (*P* < 0.001).

patients, and our results may have been influenced by selection bias. Therefore, a multicenter prospective trial needs to be performed to confirm the risk factors of ESD related to underlying disease.

CONCLUSION

Gastric ESD is feasible and permissible in elderly patients aged ≥ 80 years. To ensure a safe procedure, meticulous preventive endoscopic hemostasis is recommended after resecting specimens > 40 mm or lesions with depressive aspects or ulceration, especially those located in the lower third of the stomach, when treating aged patients. Concerning their long-term prognosis, male gender and CCI > 1 are negative predictors.

ARTICLE HIGHLIGHTS

Research background

Endoscopic submucosal dissection (ESD) is increasingly performed in elderly patients with early gastric cancer (EGC).

Research motivation

Whether gastric ESD is safe and suitable for elderly patients, type of lesions which carry an increased risk of procedure-related complications, indicators of prognosis for elderly patients after ESD are unclear.

Research objectives

To investigate short-term and long-term outcomes of gastric ESD for elderly patients, and to determine the risk factors of procedure-related complications and the indicators of prognosis.

Research methods

This study included patients aged ≥ 80 years who underwent ESD for EGC in Kanagawa Cancer Center Hospital. These patients were studied retrospectively to evaluate short-term outcomes and survival of gastric ESD.

Research results

The *en bloc* dissection rate was as high as 97.1%, and the complication rates of bleeding, perforation and aspiration pneumonitis were as low as 3.4%, 1.1% and 0.6%, respectively, which were similar to the rates of ESD for nonelderly patients. A dissection incision > 40 mm, lesions associated with depressions, and lesions with ulcers were risk factors for bleeding, and location of the lesion in the upper third of the stomach was a risk factor for perforation ($P < 0.05$). The overall survival (OS) did not differ significantly between curative and noncurative ESD groups ($P = 0.69$). In patients without additional surgery, OS rate was significantly lower in patients with a high Charlson comorbidity index (CCI) ≥ 2 than in patients with a low CCI ≤ 1 ($P < 0.001$).

Research conclusions

Gastric ESD is feasible even in elderly patients aged ≥ 80 years. Meticulous preventive endoscopic hemostasis after resecting specimens > 40 mm, or lesions associated with depressions or ulcers is recommended. CCI is a prognostic indicator. Observation without additional surgery after noncurative ESD is reasonable, especially in elderly patients with CCI ≥ 2.

Research perspectives

As our institution is a hub hospital specializing in cancer treatment, relatively healthy patients without severe underlying diseases tend to visit the hospital. Therefore, a selection bias of target patients may have existed in our study. A multicenter prospective trial with a large number of patients is desirable to confirm the feasibility of gastric ESD in patients with various health problems, and the risk factors and the prognostic indicators related to each underlying disease.

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FRONTIER

Peroral cholangioscopy: Update on the state-of-the-art

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Abstract

Peroral cholangioscopy (POC) is an endoscopic procedure that allows direct intraductal visualization of the biliary tract. POC has emerged as a vital tool for indeterminate biliary stricture evaluation and treatment of difficult biliary stones. Over several generations of devices, POC has fulfilled additional clinical needs where other diagnostic or therapeutic modalities have been inadequate. With adverse event rates comparable to standard endoscopic retrograde cholangioscopy and unique technical attributes, the role of POC is likely to continue expand. In this frontiers article, we highlight the existing and growing clinical applications of POC as well as areas of ongoing research.

Key Words: Peroral cholangioscopy; SpyGlass™; Difficult bile duct stones; Indeterminate biliary strictures; Cholangioscope-guided biopsy; Cholangioscope-guided lithotripsy

Core Tip: Cholangioscopy is an endoscopic technique that was first developed in the 1970s as a minimally-invasive modality for the evaluation of various biliopancreatic pathologies. Since the advent of the digital single-operator cholangioscopy (D-SOC) in 2015 as well as other, complementary advancements in the field, diagnostic and therapeutic applications have further expanded. Herein, we discuss the various current

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applications of cholangioscopy, with a focus on D-SOC, and areas of ongoing research to better understand potential future directions.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) was first reported in 1968 as a method to cannulate the major duodenal papilla[1]. It is now widely utilized as the primary interventional modality for many biliopancreatic disorders. Despite its vast utility, ERCP technique relies on indirect visualization of the biliary tree *via* fluoroscopy; this can be limiting for certain diagnostic and/or therapeutic applications (*e.g.* evaluation of biliary strictures, mapping of intraductal tumors for operative planning, tumor-directed ablative therapy, *etc.*).

In order to provide direct visualization of the biliopancreatic tree, peroral cholangioscopy (POC) was introduced in the 1970s[2,3]. POC was originally designed as a "mother-baby" system that required two endoscopists to operate the "mother" duodenoscope and "baby" cholangioscope[2]. In addition to the multi-operator requirement, there was a notable deficiency in this setup in the ability to acquire tissue following visualization, thus further limiting its use. Moreover, the initial scopes provided only two-way tip deflection, were fragile, and costly[4].

Over the past several decades, technologic improvements in the equipment utilized for POC has led to more widespread adoption and a growing number of applications (Figure 1). In the early 2000s, a new single-operator duodenoscope-assisted cholangioscopy technique utilizing a Pentax cholangioscope (FCP-8P/FCP-9P, Pentax Precision Instruments, Orangeburg, New York, United States) was introduced. However, this technique required the use of an endoscopist-worn breastplate to mount the cholangioscope, which allowed for manipulation of the duodenoscope with the left hand and the cholangioscope with the right hand[5]. In 2005, Boston Scientific released the first commercially available single-operator cholangioscopy (SOC) system (SpyGlass™, Boston Scientific Corporation, Natick, MA, United States), a catheter-based system that utilizes an optical probe inserted through the duodenoscope working channel[6]. Ten years later, a digital SOC (D-SOC) system was introduced (SpyGlass™ DS, Boston Scientific Corporation)[6]; this updated digital system brought improvements in image size and quality, a wider field of view, and a redesigned working channel allowing for larger diameter cholangioscopic accessories, among other changes[4,7]. In 2018, a third generation SpyScope™ DSII Catheter (Boston Scientific Corporation) featuring increased resolution and improved lighting was introduced alongside new cholangioscopic accessories. Alternatively, direct POC (DPOC) can be performed utilizing a modern ultraslim upper endoscope that can be advanced into the biliary tree following endoscopic sphincterotomy, a technique first published in a pilot study in 2006[8-10]; however, this setup is primarily used outside the United States and available in only select markets[7].

Given the recent technologic advancements in POC, its array of accessories (Figure 2), and improved training of advanced endoscopists, there has been wide propagation of this technique across most large medical centers. In this Frontiers article, we aim to underscore the major developments in the growing body of literature on POC, with particular emphasis on SOC and D-SOC, including diagnostic and therapeutic applications as well as established and investigational indications.

COMMON APPLICATIONS OF CHOLANGIOSCOPY

Management of difficult biliary stones

Approximately 10%-18% of patients with symptomatic cholelithiasis will have concomitant choledocholithiasis[11]. The standard of care for these patients is ERCP

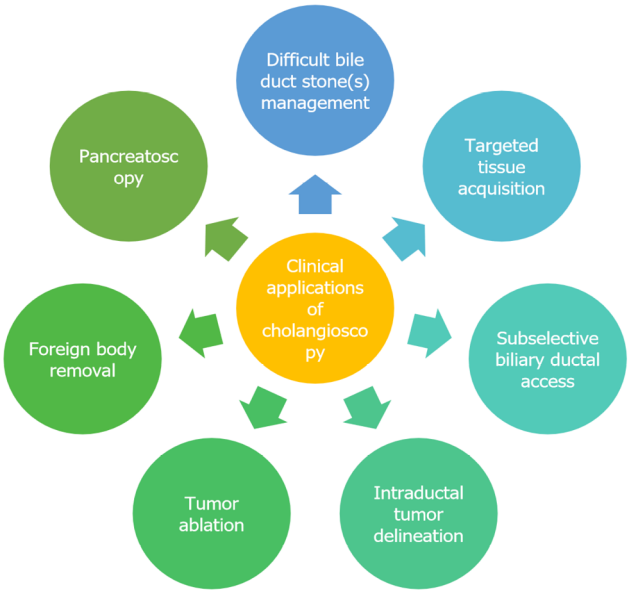

Figure 1 Common diagnostic and therapeutic applications of cholangioscopy.

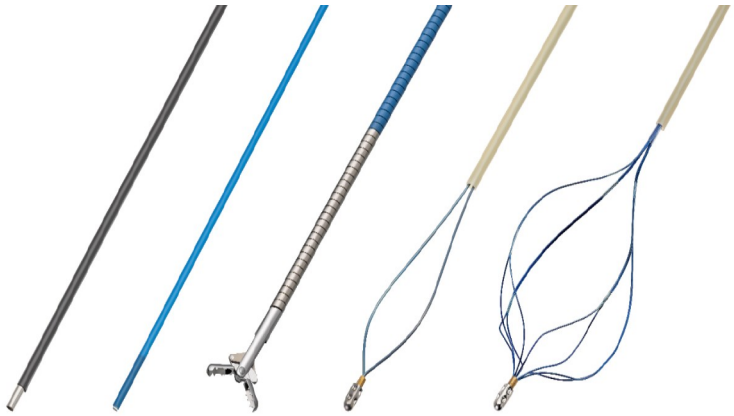

Figure 2 SpyGlass™ DS accessories including: Autolith™ Touch biliary electrohydraulic lithotripsy probe, Lumenis SlimLine™ SIS GI™ holmium laser lithotripsy probe, SpyBite™ Max biopsy forceps, SpyGlass retrieval snare, and SpyGlass retrieval basket (left to right). Additional accessories are expected to be developed over time[83]. Image adapted with permission from Dr. Isaac Raijman and Boston Scientific. Citation: **Boston Scientific Corporation.** An Expanding Suite of Compatible Accessories and Applications. [cited June 23, 2021]. Available from: https://www.bostonscientific.com/en-EU/products/direct-visualization-systems/spyglass-ds-direct-visualization-system/accessories-and-applications.html. Copyright© 2022. Published by SpyGlass™ DS.

with endoscopic sphincterotomy followed by stone extraction with a balloon or basket [4,11]. In a minority of cases, bile duct stones may be more difficult to extract, requiring additional measures[12]. Difficult bile duct stones have been previously defined as large size (> 1.5 cm in diameter), impacted stones in the bile or cystic duct, intrahepatic location, hard stone consistency, stricture distal to stones, and/or anatomical variants (*e.g.* unusual size/shape of bile duct) posing technical challenges [12,13].

POC allows for direct visualization and decreased risk of bile duct injury and is a vital addition to the ERCP armamentarium for stone disease. Indeed, a recent meta-analysis found the estimated success rate for difficult bile duct stone clearance to be 88% [95% confidence interval (CI): 85%-91%] across 820 patients (n = 31 studies)[14]. Furthermore, POC was found to have a low adverse event (AE) rate of 7% (95%CI: 6%-95%), comparable to ERCP[14,15]. Thus, POC is a valuable modality in addition to or in lieu of conventional ERCP methods such as mechanical lithotripsy (ML) and endoscopic papillary large balloon dilation (EPLBD).

Since the time of publication of the aforementioned meta-analysis, three randomized controlled trials (RCTs) comparing POC-guided electrohydraulic lithotripsy (EHL) or holmium laser lithotripsy (LL) *vs* conventional therapy (*i.e.* ML,

EPLBD, and balloon extraction) have been published. In the first study, the investigators randomized patients with bile duct stones > 1 cm in diameter in a 2:1 ratio to SOC-guided LL *vs* conventional therapy. Stone clearance was achieved in 39 of 42 (93%) patients treated with SOC-guided LL compared to 12 of 18 (67%) treated with conventional therapy (P = 0.009). AE rates were similar in the two treatment groups [16]. In the second study, successful stone removal did not differ in the SOC-guided EHL arm (37 of 48) *vs* conventional therapy arm (36 of 50) (P > 0.05); similarly, crossover yielded non-statistically significant differences in the two groups (successful stone removal in 40 of 47 patients *vs* 42 of 44 patients, P > 0.05)[17]. In the final study, the investigators randomized 32 patients with large CBD stones in whom sphincterotomy and/or EPLBD had failed into ML or D-SOC-guided LL treatment arms. Crossover was permitted as a rescue treatment if the primarily assigned technique failed to achieve stone clearance. Stone clearance rates for ML and D-SOC-guided LL groups were 63% and 100%, respectively (P < 0.01). In six patients, ML was considered a failure; when crossed over to LL, four of these patients achieved stone clearance in the same session, and the remaining two patients achieved stone clearance in subsequent LL sessions. AEs were reported at similar rates, 13% in the ML group and 6% in the LL group (P = 0.76). The median length of hospital stay following the respective procedures was 1 d in both groups (P = 0.27). At six months follow-up, neither group had recurrent cholangitis or evidence of recurrent CBD stones[18]. While the RCT data presented above may appear mixed or only partially in favor of POC in the management of difficult bile duct stones, it is important to note that only the last of the three studies discussed above utilized the newer generation of D-SOC. Thus, additional RCT data using the contemporary D-SOC system is needed.

POC can also be utilized to confirm stone clearance in cases of choledocholithiasis. In a retrospective study of 36 patients who underwent ERCP with EPLBD for difficult biliary stones, DPOC was performed immediately after a negative balloon-occluded cholangiography[19]. In 31 of 36 patients (86%), technical success was achieved with hepatic hilum visualization. Residual stones were found in 7 of these 31 patients (22.5%) upon DPOC, among which 4 patients underwent successful stone extraction during the same DPOC session. The remaining 3 patients underwent secondary ERCP for residual stone removal. There were no reported AEs in the study.

Indeterminate biliary strictures

Visual evaluation: Another major indication for POC is the evaluation of indeterminate biliary strictures (IDBSs). IDBSs are defined as biliary strictures of persistent unclear etiology following cross-sectional imaging and evaluation by ERCP with brush cytology or intraductal biopsies[20]. In a meta-analysis of 16 studies including 1556 patients, the overall sensitivity of conventional cytology from ERCP was found to be 41.6% (99%CI: 38.4%-44.8%), with a negative predictive value of 58.0% (99%CI: 54.8%-61.2%)[21]. This study and others, as well as widespread clinical experience, attest to the need for improved diagnostic capability for IDBSs.

The visual diagnosis of intraductal lesions can be aided by direct visualization during POC (Figure 3). Currently, there is no widely accepted classification system for visual diagnosis; however, some cholangioscopic findings are highly suggestive of malignancy in the appropriate clinical context. These findings include the presence of neovascularization, mucosal changes and projections, and intraductal nodules, among others[22-24]. Historically, neovascularization, also termed "tumor vessels," has had the most consensus regarding its description and malignant implications[24]. It has been described as irregularly dilated, tortuous, and abnormally proliferating vessels on the mucosa adjacent to a stricture.

In a recent systematic review and meta-analysis of 21 studies examining the diagnostic performance characteristics of POC-based visual assessments of IDBSs, the pooled sensitivity and specificity for establishing a malignancy diagnosis were 88% (95%CI: 83%-91%) and 95% (95%CI: 89-98%), respectively[25]. Subgroup analysis of studies that utilized D-SOC found a higher sensitivity for visual diagnosis [94% (95%CI: 89%-97%)] compared to D-SOC-guided biopsy [79% (95%CI: 72%-84%), P < 0.001] while also showing a higher specificity for D-SOC-guided biopsy [100% (95%CI: 97%-100%)] compared to D-SOC visual impression [86% (95%CI: 76%-92%), P < 0.001] [25]. Subgroup analysis of studies that utilized DPOC did not reveal statistically significant differences in performance characteristics of visual impression *vs* DPOC-guided biopsy (possibly suggesting superior optical performance of DPOC compared to D-SOC), though power was limited[25]. Overall, performance characteristics of visual impression utilizing modern POC (both D-SOC and DPOC) appears promising.

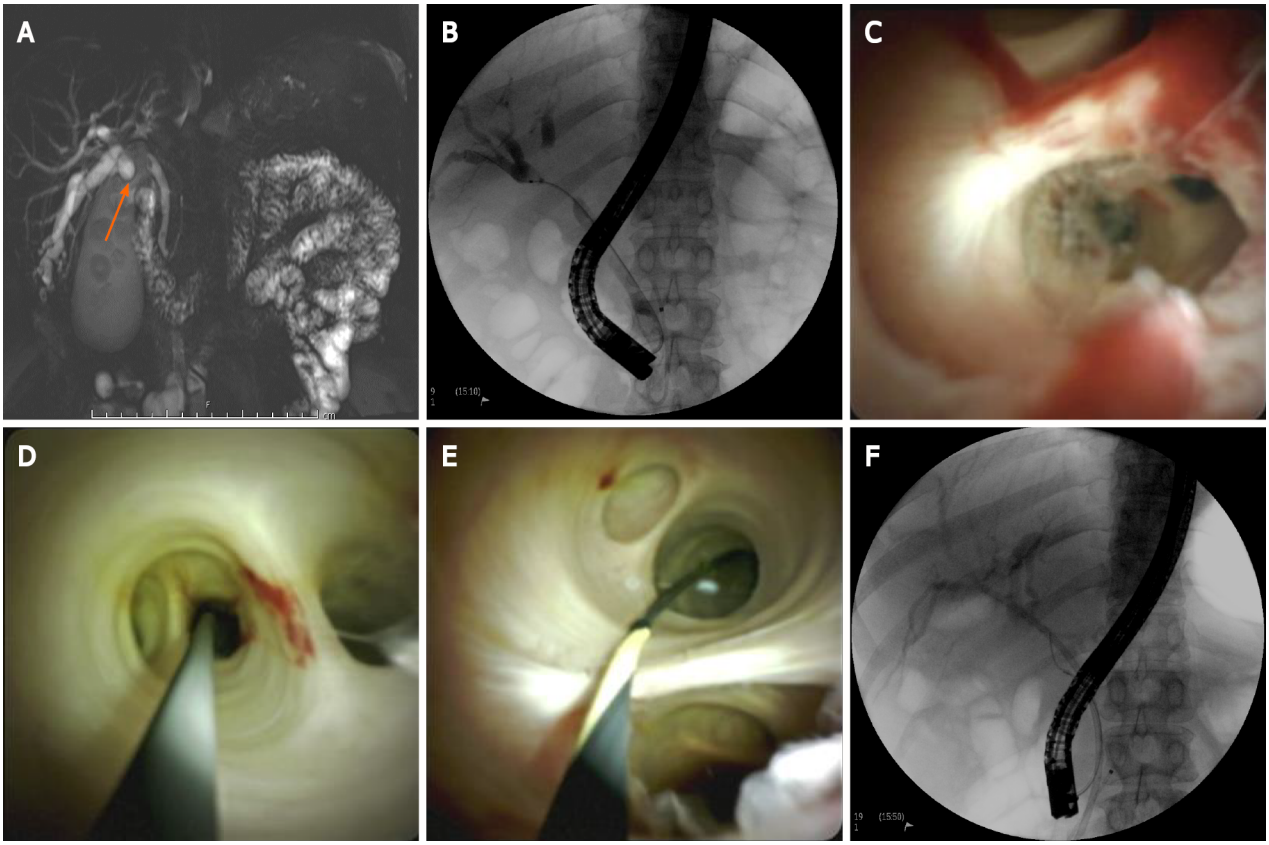

Figure 3 Example of an indeterminate biliary stricture further evaluated by cholangioscopy, initially thought to be Mirizzi syndrome secondary to chronic choledocholithiasis. A: Magnetic resonance cholangiopancreatography (T2 HASTE, coronal projection) demonstrating cholelithiasis, choledocholithiasis, and right hepatic ductal dilation as well as possible common hepatic duct (CHD) obstruction (arrow); B: Endoscopic retrograde cholangiopancreatography (ERCP) showing 1.5 cm CHD stricture suspicious for perihilar cholangiocarcinoma (CCA); C: Frond-like growth and neovascularization suggestive of neoplasm involving the CHD, later confirmed as perihilar CCA following SpyBite™ Max biopsy (previously with negative cytology on initial ERCP); D and E: Multiple views of the hepatic ducts that demonstrate scant reactive changes (from prior plastic biliary stent) and proximal limit of disease extension/tumor mapping; F: ERCP confirming successful deployment of plastic biliary stent across CHD stricture and subsequent decompression of right hepatic duct.

A recent group of researchers have produced a new schema, the "Monaco Classification," in order to attempt to standardize visual criteria in evaluating IDBSs as malignant *vs* benign. Twelve expert biliary endoscopists from around the world reviewed 40 video clips (13 benign pathology, 27 malignant) in order to consolidate visual criteria into the following: (1) Presence of stricture (symmetric or asymmetric); (2) Presence of lesion (with associated mass, nodule, or polypoid in appearance); (3) Smooth or granular mucosal features; (4) Papillary projections; (5) Ulceration; (6) Abnormal vessels; (7) Scarring (local or diffuse); and (8) Pronounced pit pattern[26]. Thereafter, 21 D-SOC video clips were reviewed by 14 interventional endoscopists utilizing these criteria, ranging from slight to moderate in interobserver agreement [26]. Diagnostic accuracy of visual interpretation of malignant *vs* benign pathology was 70% based on the new criteria, compared to an average accuracy less than 50% on prior attempts to establish visual criteria[26,27]. While the Monaco Classification has taken a crucial step in a forward direction, it would benefit from further refinement and validation.

Cytopathologic evaluation: In addition to the visual diagnosis of IDBSs, POC-guided biopsy can provide further histopathologic interpretation of IDBSs. In a systematic review with meta-analysis of 10 studies evaluating the use of SOC-guided biopsy for the diagnosis of malignant biliary strictures, the overall pooled sensitivity and specificity were 60.1% (95%CI: 54.9%-65.2%) and 98.0% (95%CI: 96.0%-99.0%), respectively[28]. In a subset of four studies, patients (n = 148) had previously undergone ERCP with benign or non-diagnostic brushing/biopsy results (with strong suspicion for malignancy); in this specific cohort, the pooled sensitivity and specificity of SOC-guided biopsy were 74.7% (95%CI: 63.3%-84.0%) and 93.3% (95%CI: 85.1%-97.8%), respectively[28]. More recently, a systematic review with meta-analysis of 11 studies examined the use of D-SOC-guided biopsy for evaluation of IDBSs. The pooled

sensitivity and specificity were 74% (95%CI: 67%-80%) and 98% (95%CI: 95%-100%), respectively[29]. These data suggest that POC-guided biopsy, in particular D-SOC-guided biopsy, yields improved diagnostic sensitivity when evaluating IDBSs.

POC-guided biopsies can be useful in cases where prior ERCP biopsies/brushings return benign or non-diagnostic results (when a strong suspicion for malignancy nevertheless remains) (Figure 3). In addition, a retrospective study of 40 patients found that biliary lavage cytology can be combined with POC-guided biopsy to further improve diagnostic sensitivity and accuracy when compared to POC-guided biopsy alone (sensitivity 88% *vs* 70% and accuracy 90% *vs* 75%, respectively)[30]. Of note, the data presented above predates the advent of the SpyBite™ Max biopsy forceps, which has increased tissue capacity compared to the first-generation SpyBite (legacy) forceps. This, along with other improvements, is expected to further improve the diagnostic performance of POC-guided intraductal biopsy.

One limiting factor that has been thought to potentially hamper the utility of SOC-guided biopsy is the absence of on-site cytopathology for real-time tissue processing, a concern recently addressed by the SOCRATES (single-operator cholangioscopy randomized trial evaluating specimens) trial[31]. In this RCT, patients (n = 62) with IDBSs were randomized to an off-site tissue processing cohort (n = 30) and an on-site cohort (n = 32) in order to compare diagnostic accuracy. The study found a diagnostic accuracy of 90% (95%CI: 73.5%-97.9%) versus 84.4% (95%CI: 67.2%-94.7%) when comparing off-site tissue processing *vs* on-site, respectively (P = 0.86). Additionally, the overall treatment costs of D-SOC based on the Medicare reimbursement fee structure (including anesthesia, hospital fees, laboratory fees, medications, supplies, and radiologic fees) was found to be $14423 for the off-site cohort compared to $13015 for the on-site cohort (P = 0.60). Thus, this RCT suggests that D-SOC is a cost-effective option for the evaluation of IDBSs, even in centers without on-site cytopathology.

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic, progressive disease that causes inflammation and fibrosis of the biliary tract, often leading to end-stage liver disease and/or cholangiocarcinoma (CCA)[32]. Patients with PSC can develop "dominant strictures," or focal narrowing defined at ERCP as stenosis with diameter ≤ 1.5 mm in the CBD and/or ≤ 1.0 mm in a hepatic duct within 2 cm of the ductal confluence[20,32-34]. Dominant strictures are clinically significant in light of their higher propensity for bacterial cholangitis and for underlying dysplasia or carcinoma[32,35]. A recent systematic review and meta-analysis of 21 studies found the that the pooled sensitivity and specificity of POC for diagnosis of CCA was 65% (95%CI: 35%-87%) and 97% (95%CI: 87%-99%), respectively[36]. POC-guided biopsy also had the highest diagnostic accuracy (96%), compared to bile duct brushings (87%), fluorescence *in situ* hybridization (FISH) (69% for polysomy and 47% for trisomy), and probe-based confocal laser endomicroscopy (75%)[36].

However, not all data to date support the use of POC in patients with PSC. For example, a prospective study of 47 patients with PSC evaluating the use of POC-guided biopsy of strictures found a significantly lower sensitivity (33%) than previously reported[37]. Additionally, a retrospective study of 92 patients, both with (n = 36) and without (n = 56) PSC, examined the performance characteristics of ERCP with brush cytology, FISH, POC-guided biopsy, transpapillary biopsy and each possible combination of the aforementioned for the detection of CCA. When combining all diagnostic modalities, patients without PSC showed a trend towards improved sensitivity compared to brush cytology alone (75% *vs* 40.9%, P = 0.06)[38]. However, the PSC group did not show a similar trend towards improved sensitivity when comparing all four diagnostic modalities to cytology alone (60% *vs* 50%, P = 1)[38].

Overall, the precise role of POC in the diagnostic evaluation of dominant strictures in PSC remains unclear. POC can potentially play an important role in studying the natural history and progression of PSC and in general facilitate better characterization and sampling of dominant strictures. For instance, with the newly proposed cholangioscopy-based "Edmonton Classification" system for phenotypic classification, dominant strictures can be classified into one of the three following phenotypes: Inflammatory, fibro-stenotic, or nodular or mass-forming. One theory is that these and other POC findings may differ by disease stage/pathobiological involvement (*e.g.* nodular or mass forming may be indicative of developing or nascent CCA)[39]. It is proposed that combining phenotypic data with histopathology, biochemical markers, and cholangiography scores over time could lead to improved management algorithms[40]. For now, validation of this classification system remains the initial step

prior to determining its ultimate clinical utility.

Evaluation of intraductal neoplasms

POC is becoming increasingly useful in the mapping of biliopancreatic neoplasms such as CCA and intraductal papillary mucinous neoplasms (IPMNs). With improved visual delineation of neoplastic margins in the biliary tree and pancreatic ducts, staging can be more precise, and thus a better-informed therapeutic plan can be formulated (Figure 3). A multicenter prospective cohort study of 118 patients evaluated the impact of cholangiopancreatoscopy on preoperative assessment of biliopancreatic neoplasms. Following cholangiopancreatoscopy, the initial therapeutic plan was altered in 34% of patients[41]. Of these patients, more extensive surgery was required in 10%, less extensive surgery was required in 65%, and surgery was avoided in the remaining 25%[41]. Additionally, the study reported a 88% correlation in histology between the surgical specimens and cholangiopancreatoscopy specimens [41].

Cholangiopancreatoscopy is also being utilized to directly examine pancreatic duct abnormalities, such as distinguishing between pancreatic duct dilation secondary to chronic pancreatitis *vs* IPMNs[42]. When used in conjunction with non-invasive imaging, POC/cholangiopancreatoscopy improves diagnostic and therapeutic ability. As has been discussed in prior sections, this is mainly from direct visual tissue inspection and the ability to obtain targeted biopsies. Simultaneously, it also offers the opportunity for facilitate therapeutic intervention (*e.g.* management of pancreatolithiasis).

Selective guidewire placement

Numerous case reports, series, and a retrospective study have all demonstrated the potential benefits of POC-guided guidewire placement across strictures of varying causes (malignant, post-OLT, PSC, *etc.*)[43-45]. In the retrospective study, a total of 23 patients with known biliary strictures in whom endoscopic guidewire placement had previously failed underwent 30 procedures; technical success (guidewire placement) was achieved in 70%[43]. Subgroup analysis demonstrated a higher technical success rate among benign biliary strictures *vs* malignant strictures (88% *vs* 46%, $P = 0.02$). Of the 23 patients, 7 underwent repeat procedures, both in patients with previous failure of guidewire placement ($n = 3$) and prior success of guidewire placement ($n = 4$). A higher technical success rate was demonstrated on initial exam compared to subsequent exams (78% *vs* 43%, $P = 0.15$)[43]. While data are limited, POC-guided guidewire placement can be an effective alternative option, though traditional ERCP approaches should be attempted primarily given the significantly higher costs associated with POC and the ability to potentially troubleshoot successfully with varying guidewire diameters, tip designs, tip core materials, *etc.* during ERCP.

Biliary tumor ablation

The use of POC-guided radiofrequency ablation (RFA) to provide locoregional cancer-directed therapy for the management of extrahepatic CCA or other intraductal malignancies has been presented in various case reports[46,47]. Historically, percutaneous RFA has been well studied, though this technique has demonstrated an association with various AEs[48]. ERCP-RFA (without POC) has thus been explored as a possible alternative in porcine models, yielding similar concerns for high AE rates [49]. In a review article, the pooled data from 12 studies evaluating endoscopic RFA treatment for the management of patients with unresectable malignant biliary strictures showed similarly high AE rates (16%) across 318 total patients[50]. In a retrospective study of 12 patients, POC-guided RFA was both technically (RFA probe insertion into stricture site) and clinically successful (tumor ablation with POC imaging) while demonstrating safety (1 AE in study population) and efficacy in maintaining stent patency (median of 154 d) following POC-guided RFA. Though data are limited, POC-guided RFA could be explored in further studies as a potentially viable, safer (compared to percutaneous RFA and endoscopic RFA) palliative treatment option for select patients with unresectable malignant biliary strictures.

POC-guided photodynamic therapy (PDT) has also been suggested to improve symptoms and prolong survival in cases of unresectable biliary tumors, with relatively few complications[51]. PDT begins with the administration of intravenous photosensitizer, which is preferentially retained by malignant tissue, approximately 24 h prior to POC. Subsequently, light energy can be delivered under POC guidance to the target tissue at a photoactivating wavelength, resulting in a photochemical reaction inducing ischemia and necrosis of tumor cells[52]. RCT data is limited to ERCP-based studies, in which PDT plus endoscopic stenting ($n = 20$) *vs* endoscopic stenting alone

(n = 19) found improvement in median survival (493 d *vs* 98 d, P < 0.0001)[53]. However, a retrospective case series (n = 45) demonstrated similar absolute increases in median survival time when comparing SOC-guided PDT *vs* PDT-only, though not statistically significant (386 d *vs* 200 d, P = 0.45)[51]. This may suggest that larger cohorts need to be studied to better understand whether the effect of SOC-guided PDT truly plays an essential role compared to PDT therapy alone.

Post-liver transplant biliary complications

One AE orthotopic liver transplantation (OLT) patients face is the development of biliary strictures, either anastomotic (more common) or nonanstomotic (less common). Biliary strictures affect up to nearly 40% of post-OLT patients[54]. In these cases, POC can be utilized for visual assessment of the biliary epithelium and/or targeted biopsy, if needed[55]. Additionally, some strictures are not amenable to guidewire insertion or cannulation with standard ERCP (*e.g.* angulated strictures)[56]; the addition of POC can facilitate guidewire insertion and possibly obviate the need for biliary drainage or surgical intervention[55,56].

In a recent observational study of 26 patients who underwent ERCP followed by POC for suspected biliary complications post-OLT, 33 biliary complications were found in 22 patients. The remaining 4 patients were found to have normal bile ducts. Of the biliary complications, anastomotic strictures were the most common (14), followed by nonastomotic strictures (7), biliary stones (6), and lastly biliary casts (3). In 12 patients (46%), POC demonstrated a clear benefit: Selective guidewire placement, identification of biliary cast and/or stones not previously found on ERCP, or epithelial changes (*e.g.* ulceration or inflammation) secondary to infection[44]. Additional case series have shown the potential benefits of POC-guided steroid injections for management of anastomotic strictures and POC-guided guidewire placement across strictures (previously failed under fluoroscopic guidance)[56,57]. All of these observational studies suggest low rates of AEs, even in the post-OLT population[44,56,57]. Of note, in immunocompromised post-OLT patients, it is important to provide a prophylactic course of antibiotics given the potential increased risk of bacterial translocation with POC[58].

Radiation-free management

One of the disadvantages of conventional ERCP therapy is radiation exposure to patients and medical staff from the use of fluoroscopy. In particular, there can be teratogenic risk posed to pregnant patients in the first trimester[59]. While ERCP remains the standard of care and every effort should be made to use fluoroscopy selectively and with proper safety measures, POC can be utilized as an alternative management strategy to minimize or obviate the use of radiation[60]. A recent retrospective, multicenter study demonstrated 100% success rate in achieving bile duct cannulation without the use of fluoroscopy in the study population of pregnant patients (n = 10) with a mean gestational age of 23 wk. Indications for intervention included: Choledocholithiasis (7), stent removal (1), biliary stricture (1), and combined choledocholithiasis/stent removal (1). Fifty-percent of patients were able to undergo a completely radiation-free procedure, while an additional 30% received a dose minimized below the recommended amount. AEs (pancreatitis[1], mild bleeding[1]) occurred in two patients (20%)[61]. The data remain limited in this cohort, but this application of POC can certainly be considered as a possibly safer alternative in select cases[61-63].

EMERGING AND MISCELLANEOUS APPLICATIONS OF CHOLANGIOSCOPY

Novel applications of POC continue to emerge. One area of demonstrated utility has been in the removal of migrated stents and other foreign bodies. Following failed retrieval attempts with ERCP, POC can provide better visualization and/or access for successful extraction, thereby avoiding more invasive procedures[64-67]. Additionally, POC can aid in the evaluation and management of hemobilia. After magnetic resonance cholangiopancreatography (MRCP) or ERCP demonstrates the presence of blood in the bile duct, POC can facilitate determining the source and etiology of bleeding. In one case report, POC was utilized to confirm hemobilia arising from the gallbladder, and ultimately a diagnosis of diffusely infiltrative gallbladder cancer was made[68]. Another case report describes the detection of biliary angiodysplasia during

POC following an unrevealing MRCP[69]. There have also been reports of the use of POC in select cases of cholecystitis, where patients may not otherwise be surgical candidates and/or in the presence of anatomical challenges. In these instances, POC can be utilized to access and traverse the cystic duct with subsequent deployment of metal or plastic stents as a means of minimally-invasive management[70-72]. Finally, there has been a reported case of POC-guided EHL for the removal of a calcified stool bezoar in an elderly patient with chronic, severe constipation[73].

DRAWBACKS OF CHOLANGIOSCOPY: ECONOMIC CONSIDERATIONS AND AEs

Though the clinical applications of POC continue to expand, several factors hinder further widespread use. In particular, the financial implications of POC *vs* conventional ERCP, owing to the high cumulative costs of the POC processor, cholangioscopes, and cholangioscopic accessories, are major hindering factors. Overall, start-up costs have been estimated to range between 50000 to $90000, though they can vary substantially by institutional contract[74]. Additionally, cholangioscopes (D-SOC) and their accessories are both single-use, and each one costs on the order of thousands and hundreds of dollars, respectively. Based on a micro-costing approach, one European study suggested that POC could be cost-effective for both treatment of difficult bile duct stones and diagnosis of IDBSs when compared to conventional ERCP[75]. However, robust economic data are lacking in the United States. Moreover, procedure times are often longer with POC when compared to conventional ERCP; thus, this may deter performance of POC due to the ability to generate more revenue with conventional ERCP *per* unit of time.

The overall AE rate associated with POC has been reported to be between 4% and 22%[76]. The major AEs include: Cholangitis, bacteremia, liver abscess, pancreatitis, and bleeding[77]. In a nationwide study in Sweden analyzing 36352 ERCP procedures and 408 cholangioscopy procedures between 2007 and 2012, reported post-procedural AEs were higher with POC when compared to ERCP (19.1% *vs* 14.0%)[78]. Pancreatitis (7.4% *vs* 3.9%) and cholangitis (4.4% *vs* 2.7%) showed similar increases, though multivariate analysis did not demonstrate a statistically significant difference when adjusted for confounders[78]. While higher rates of AEs with POC remain a concern, one group found that administration of peri-interventional antibiotics can substantially reduce rates of cholangitis[79]. With ongoing evolution of POC technology, its safety profile when directly compared to conventional ERCP will need continued assessment.

RECENT AND FUTURE DEVICE DEVELOPMENT

In May 2019, a next generation "mother-baby" videocholangioscope system (CHF-B290, Olympus Medical Systems Corporation, Tokyo, Japan) was introduced[80,81]. Despite being a newer iteration with notable improvements, some previously known limitations (*e.g.* two endoscopist operators and two equipment towers) remain, while others, such as scope fragility and accessory channel diameter, have been reported to be improved[80]. Currently, this system is only available for use in certain markets in Asia and Europe[80].

In July 2020, Ambu Inc. received FDA approval for the Ambu® aScope™ (Ambu Inc, Columbia, MD United States) Duodeno, a single-use duodenoscope. It is anticipated that a single-use cholangioscope and additional accessories will follow in the next 1-2 years, with the potential for new clinical applications. It will be interesting to compare these developments to existing scopes and accessories.

CONCLUSION

With growing evidence to support its use, POC has evolved into an important tool in the biliopancreatic armamentarium. It is an important therapeutic option for difficult biliary stones and a core part of the evaluation of indeterminate strictures. Outcomes from the use of D-SOC for other ongoing and investigational indications (*e.g.* radiation-free intervention in pregnant patients, migrated stent/foreign body extraction, post-OLT biliary complication management, and selective guidewire

placement) appear promising. Still, as discussed in this review, there are constraining factors and limitations to consider, *e.g.* device costs, paucity of standardized cholangioscopic visual classification systems, anatomical challenges, *etc.*[82].

In the future, further research and data are needed to solidify the evidence for POC and clarify the outcomes of its investigational applications. For now, endoscopists may continue to explore additional frontiers of clinical application, particularly with the advent of new accessories and further technologic enhancements that may be on the horizon.

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MINIREVIEWS

Exposed endoscopic full-thickness resection for duodenal submucosal tumors: Current status and future perspectives

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Abstract

Exposed endoscopic full-thickness resection (EFTR), with or without laparoscopic assistance, is an emergent natural orifice transluminal endoscopic surgery technique with promising safety and efficacy for the management of gastrointestinal submucosal tumors (SMTs) arising from the muscularis propria (MP), especially of the gastric wall. To date, evidence concerning duodenal exposed EFTR is lacking, mainly due to both the technical difficulty involved because of the special duodenal anatomy and concerns about safety and effectiveness of transmural wall defect closure. However, given the non-negligible morbidity and mortality associated with duodenal surgery, the recent availability of dedicated endoscopic tools for tissue-approximation capable to realize full-thickness defect closure could help in promoting the adoption of this endosurgical technique among referral centers. The aim of our study was to review the current evidence concerning exposed EFTR with or without laparoscopic assistance for the treatment of MP-arising duodenal SMTs.

Key Words: Endoscopic full-thickness resection; Exposed endoscopic full-thickness resection; Laparoscopy-assisted endoscopic full-thickness resection; Duodenal submucosal tumors; Novel oral transluminal endoscopic surgery

Core Tip: Exposed endoscopic full-thickness resection (EFTR) is a promising minimally invasive alternative to surgery for the removal of gastrointestinal

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submucosal tumors (SMTs) originating from the muscularis propria. To date, evidence concerning duodenal exposed EFTR is lacking, mainly due to both the technical difficulty and concerns about an effective closure of the transmural defect. However, given the non-negligible morbidity and mortality associated with duodenal surgery, the recent availability of dedicated endoscopic devices able to achieve a full-thickness defect closure could help in overcoming these concerns. Our study aimed to review the current evidence regarding exposed EFTR for deep duodenal SMTs.

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INTRODUCTION

Though relatively infrequent, the diagnosis of duodenal submucosal tumors (D-SMTs) has increased due to the widespread use of gastrointestinal endoscopy[1,2]. D-SMTs originating from the submucosa and from the muscularis propria (MP) include lesions with malignant potential, such as gastrointestinal stromal tumors (GISTs) and neuroendocrine tumors (NETs)[3,4].

According to current guidelines, either suspected or histologically proven GISTs larger than 20 mm in diameter or with high-risk endoscopic ultrasonography (EUS) features (*i.e.*, irregular borders, cystic spaces, ulcerations, echogenic foci and heterogeneity) should be removed with histologically negative margins. Given the limited intramural extension of GISTs and their rare lymph node involvement, surgical local resection without additional lymphadenectomy is currently regarded as the gold standard of treatment[4-6]. Furthermore, resection of gastric NETs ≥ 10 mm in diameter is recommended, while all duodenal NETs should be excised, regardless of their size[7]. However, traditional duodenal surgery, such as open pancreaticoduodenectomy (PD), carries a significantly higher risk of morbidity and mortality compared to that for other gastrointestinal (GI) sites[8]. Moreover, various types of laparoscopic limited resection of the duodenum have been reported, including laparoscopic wedge resection, laparoscopic and endoscopic cooperative surgery, and laparoscopic segmental duodenectomy[9,10]. Though less invasive, they are technically challenging due to the retroperitoneal anatomical location of the duodenum and its intimate relationship with the pancreas, ampulla of Vater, and distal common bile duct. Thus, conversion to PD may be required[11].

In this setting, endoscopy may offer the chance for a minimally invasive curative approach for D-SMTs. Safe and effective removal of small D-SMT without involvement of the MP by means of endoscopic mucosal resection (EMR) has been reported [4]. Furthermore, though endoscopic submucosal dissection (ESD) within the duodenum is not routinely recommended due to high risk of perforation, its adoption for the treatment of duodenal lesions has been reported, with good outcomes across referral centers[12-14]. However, MP-originating D-SMTs cannot be completely removed by means of EMR or ESD, due to both MP layer involvement and adherence to serosa. ESD-assisted exposed endoscopic full-thickness resection (EFTR) is a scarless natural orifice transluminal endoscopic surgery (NOTES) procedure with a reported good safety and efficacy profile, particularly for the treatment of MP-originating gastric submucosal tumors (G-SMTs)[15,16]. However, there is a lack of evidence regarding duodenal exposed EFTR, due to technical difficulty related to the complex duodenal anatomy and concerns about a safe and effective closure of the transmural defect[17]. Nevertheless, duodenal perforation is associated with higher morbidity and mortality compared with those occurring within other GI sites[18].

The aim of our study was to review the current evidence concerning exposed EFTR with or without laparoscopic assistance for the treatment of MP-originating D-SMTs.

LITERATURE SEARCH

A literature search by using PubMed (MEDLINE) and EMBASE for the period January 1998 (the year EFTR was first reported) to February 2021 was undertaken in order to identify relevant studies on duodenal ESD-assisted exposed EFTR, with or without laparoscopic assistance. The search strategy usedthe following terms: "Endoscopic full-thickness resection," "EFTR," "exposed endoscopic full-thickness resection," "laparoscopy assisted endoscopic full-thickness resection," and "LAEFR." The literature search was limited to human studies and English language. Meeting abstracts were excluded. Articles reporting on both LECS procedures, in which tumor resection is mainly performed surgically, and non ESD-assisted EFTR were also excluded from the current review. The references of review articles and relevant papers were hand-searched to identify any additional studies.

ROLE OF EXPOSED EFTR IN THE MANAGEMENT OF MP-ORIGINATING D-SMTS

Technique

Exposed EFTR is a "cut then close" technique carrying out full-thickness excision with the creation of an intentionalperforation, followed by wall defect suture. Thus, the term "exposed" is derived from the temporary peritoneal exposure to the GI contents [19].

The exposed EFTR technique was first described by Ikeda *et al*[20] in a porcine stomach in 2006[20], and finally translated into clinical practice by Zhou *et al*[21] a few years later[21]. The principal procedures of ESD-assisted exposed EFTR are as follows [4]: (1) Circumferential mucosal and submucosal incision around the lesion by means of typical ESD technique; (2) Muscular and serosal incision, pursuing an active perforation; and (3) Endoscopic closure of the resulting transmural wall defect. Alternatively, post-EFTR defect closure by means of laparoscopic hand-suturing has been reported in the laparoscopy-assisted endoscopic full-thickness resection (LAEFR)[22].

The exposed ESD-assisted EFTR without laparoscopic assistance technique is illustrated in Figure 1.

Evidence

In 2012, Abe *et al*[22] reported the first case of LAEFR for a 10 mm carcinoid tumor of the duodenal bulb. Resection with histologically negative margins was accomplished, and the duodenal post-EFTR wall defect was sutured laparoscopically by means of an Albert anastomosis. No major adverse events were reported. Of note, during the same operative session laparoscopic lymphadenectomy was done before the EFTR, with intra-operative histological examination showing the absence of metastatic tumor cells [23].

In a multicenter prospective cohort study enrolling 42 patients undergoing gastrointestinal exposed EFTR, five procedures performed for SMTs located in the duodenal bulb were also included. The resulting post-EFTR transmural defect was effectively closed by the application of pursestring sutures with nylon loops and clips in all cases, and no major adverse events were observed[24].

A large retrospective study evaluated the efficacy and safety of exposed EFTR without laparoscopic assistance in 32 patients with non-ampullary MP-arising duodenal SMTs. With regard to post-EFTR defect closure, various endoscopic techniques were adopted (Table 1). In one case, endoscopic closure of a 2.5 cm post-EFTR defect located at the anterior wall of the bulb-descending junction appeared technically unfeasible; thus, conversion to open surgery was undertaken, with successful defect suture. Complete resection was achieved in all cases, and no recurrence was observed during a mean follow-up period of 38 mo. The occurrence of major adverse events was reported in two of 32 procedures. A case of EFTR performed for a 2.5 cm lesion in the anterior wall of the bulb-descending junction with defect closure by means of endoloops and clips was complicated by delayed perforation. Laparoscopic exploration with drainage tube placement was performed, and the patient was discharged on post-operative day 6. Finally, in a male patient aged 81, with a history of chronic obstructive pulmonary disease post-operative decline in blood oxygen saturation was observed. The patient was transferred to the intensive care unit and successfully treated conservatively[25].

Table 1 Summary of studies reporting on duodenal endoscopic submucosal dissection-assisted exposed endoscopic full-thickness resection

Ref.	Study design	Lesions, *n*	Mean size (range), cm	Site	R0	Histology	Surgical conversion	Closure method	Mean operation time (range), min	Major AEs	Mean poLOS (range), days	Mean follow-up (range), months	Recurrence
Abe *et al* [23], 2012	CR	1	1.0	Bulb: Anterior wall		Carcinoid	0	Laparoscopic hand-suturing	200	0	7	-	-
Qiao *et al* [24], 2018	R	5	-	Bulb	-	-	0	EPSS	-	0	4.5	12	0
Ren *et al* [25], 2019	R	32	1.2 (0.5–3.0)	Bulb: Anterior wall (*n* = 21); posterior wall *via* (*n* = 1); Bulb-D2 junction: Anterior wall (*n* = 8); D2 (*n* = 2)	32	GIST (*n* = 14); NET (*n* = 4); Heterotopic pancreas (*n* = 11); Leiomyoma (*n* = 2); Lipoma (*n* = 1)	2	Clips (*n* = 6); Clips + endoloops (*n* = 20). Clips + endoloops + fibrin glue (*n* = 4); ESS (*n* = 1)	-	Delayed perforation (*n* = 1); SO2 decline (*n* = 1)	6.2 (2–19)	38 (14–73)	0
Yuan *et al* [26], 2019	CR	1	2.0	Bulb	1	GIST	0	EPSS	55	0	4	3	0
Granata *et al*[27], 2021	R	2	2.4 (1.8–3.0)	Bulb: Anterior wall (*n* = 1); inferior wall (*n* = 1)	2	GIST (*n* = 1); NET (*n* = 1)	0	ESS	293 (145–148)	0	3.5 (3–4)	15 (12–18)	0

AEs: Adverse events; poLOS: Post-operative length of stay; CR: Case report; R: Retrospective; D2: Descending duodenum; GIST: Gastrointestinal stromal tumor; NET: Neuroendocrine tumor; SO2: Oxygen saturation; EPSS: Endoscopic purse-string suture; ESS: Endoscopic suturing system.

In 2019, Yuan *et al*[26] reported a case of successful exposed EFTR without laparoscopic assistance performed for a 20 mm duodenal bulb low-grade GIST. The resulting transmural wall defect was effectively closed with endoloops and endoclips using the purse-string suture technique. R0 resection was achieved, no major adverse events were observed, and the patient was discharged home on post-operative day 4[26].

Finally, in a recent retrospective case series from Italy, two exposed EFTR procedures of the duodenal bulb were reported. Wall defect closure was successfully performed by means of the OverStitch Endoscopic Suturing System (Apollo Endosurgery, Austin, Texas, United States). Histological examination showed free resection margins in both cases (1 NET, 1 GIST) and no major adverse events were encountered[27].

Results of the included studies in which duodenal ESD-assisted exposed EFTR was performed are summarized in Table 1.

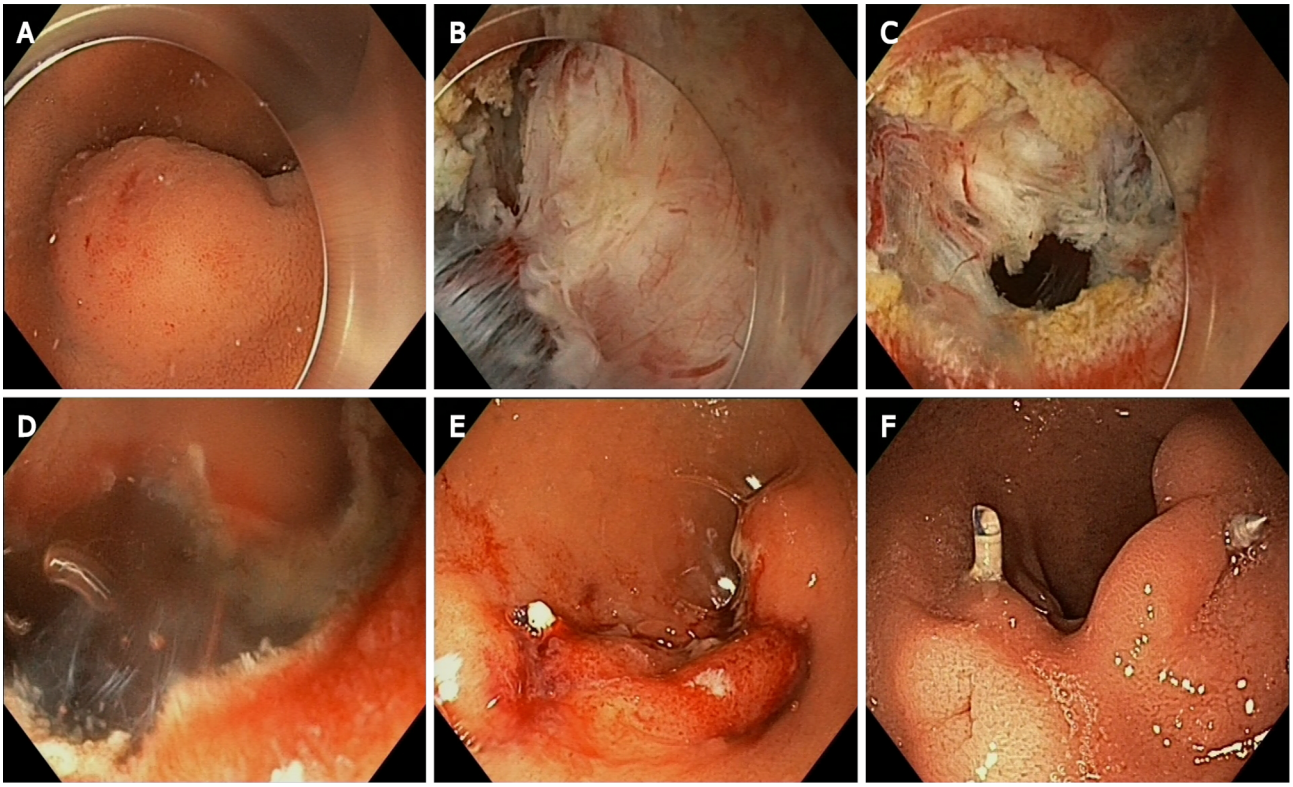

Figure 1 Duodenal exposed endoscopic full-thickness resection without laparoscopic assistance with defect closure using endoscopic suturing system. A: Endoscopic view of a submucosal lesion located in the duodenal bulb; B: Circumferential mucosal and submucosal incision; C: Exposed endoscopic full-thickness resection of the tumor and creation of "active perforation"; D: Transmural defect of the duodenal bulb; E: Full-thickness defect closure by means of OverStitch endoscopic suturing system; F: Endoscopic view of the resection site on post-operative day 60.

CONCLUSION

To date, the optimal resection modality for the treatment of MP-originating D-SMTs has not been established. PD carries a high rate of morbidity[8,11], while pancreas-preserving limited duodenal resection techniques are technically challenging, with a non-negligible rate of conversion to PD[9,11]. Furthermore, both EMR and ESD techniques are technically unsuitable for the complete resection of D-SMTs arising from the MP and adhering to the serosa layer, being limited to mucosal and submucosal layer, respectively. Intriguingly, non-exposed EFTR have been proposed for the resection of deep D-SMTs, with promising outcomes[28]. With the use of this "close then cut" technique, the lesion is resected after the GI wall patency is secured by creation of full-thickness wall duplication. Non-exposed EFTR can be realized with the use of a dedicated full-thickness resection device (FTRD; Ovesco Endoscopy, Tuebingen, Germany), consisting of an over-the-scope clip (OTSC) preloaded into a cap with an integrated snare. Alternatively, the application of an OTSC (OTSC, Ovesco Endoscopy GmbH, Tuebingen, Germany; Padlock Clip, Aponos Medical, Kingston, NH, United States) is followed by excision of the created pseudopolyp by the use of a snare or a needle knife. Non-exposed EFTR provides the potential avoidance of both peritoneal dissemination of tumor cells and extraluminal spillage of gastrointestinal content. In addition, this approach is technically much easier and faster to perform. However, this technique has a lower R0 resection rate than exposed EFTR. This is probably due to the technical unfeasibility of a "real-time" and direct visualization of the circumferential cutting margins. Furthermore, OTSC cannot be repositioned after its deployment, and non-exposed EFTR is reserved for smaller lesions (< 25 mm)[19,28].

In this scenario, ESD-assisted exposed EFTR with or without laparoscopic assistance could replace traditional surgery for the radical treatment of select cases of deep D-SMTs. However, evidence concerning the use of this NOTES procedure for D-SMTs is lacking. Traditionally, the duodenum has been considered a "forbidden" zone for exposed EFTR mainly due to technical difficulties related to complex anatomic relationships with surrounding organs and vessels, a narrow lumen, and a "C-loop," resulting in troublesome maintenance of the desired endoscope position. Hence,

concerns about an effective and reliable post-EFTR transmural defect closure must be raised.

Delayed perforation of the duodenum is associated with higher morbidity and mortality than other GI sites[8]. However, the recent development of dedicated endoscopic devices for tissue-approximation capable of achieving a full-thickness "surgical-quality" defect closure, such as the OverStitch Endoscopic Suturing System and OTSC systems, could help in overcoming these concerns[29,30].

In our opinion, a step-up approach with exposed EFTR as the first-line of treatment for selected deep D-SMTs appears particularly intriguing. Its adoption should be reserved for non-periampullary MP-originating D-SMTs up to 30 mm in diameter and without predominant extraluminal growth pattern, and limited to highly experienced centers. Full-thickness closure of the post-EFTR wall defect is strongly advised.

High morbidity and mortality associated with duodenal surgery justify active research in this field. Further large prospective studies in high-volume referral centers are needed to better clarify the role of exposed EFTR with or without laparoscopic assistance for the treatment of MP-arising D-SMTs.

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MINIREVIEWS

Endoscopic colorectal cancer surveillance in inflammatory bowel disease: Considerations that we must not forget

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Abstract

Inflammatory bowel disease (IBD), encompassing Crohn's disease and ulcerative colitis, is a chronic immune-mediated inflammatory disease that primarily affects the gastrointestinal tract and is characterized by periods of activity and remission. The inflammatory activity of the disease involving the colon and rectum increases the risk of colorectal cancer (CRC) over the years. Although prevention strategies are evolving, regular surveillance for early detection of neoplasia as a secondary prevention strategy is paramount in the care of IBD patients. In this review article, we discuss the current evidence of the risks of developing CRC and evaluate the best available strategies for screening and surveillance, as well as future opportunities for cancer prevention.

Key Words: Inflammatory bowel disease; Endoscopy; Crohn's disease; Ulcerative colitis; Surveillance; Colorectal cancer

Core Tip: Colorectal cancer (CRC) is one of the leading causes of death in inflammatory bowel disease (IBD) today. However, subsequent reports have shown lower rates of CRC. The expanding medical options in IBD have substantially improved our ability to control severe inflammation and likely to reduce the risk of CRC in this setting. We discuss the current evidence of the risks of developing CRC, and evaluate

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, progressive or relapsing and remitting immune-mediated condition of the intestines[1,2]. While the pathogenesis has not been fully elucidated, it is generally considered a consequence of a dysregulated immune response to environmental triggers in genetically predisposed subjects[3,4]. CRC is a major cause of death in IBD, accounting for 10 to 15% of death in IBD[5,6]. CRC risk increases over time after IBD diagnosis. In ulcerative colitis (UC), a prior meta-analysis estimated the CRC risk to be 2%, 8%, and 18% at 10, 20, and 30 years, respectively, after disease diagnosis[7]. This risk is also higher in patients with long-standing and diffuse colonic CD [relative risk (RR) of 4.5 (95%CI: 1.3-4.9)][8]. However, later reports have shown lower rates of left-sided CRC of 2.5%, 7.6%, and 10.8% at 20, 30, and 40 years after diagnosis, respectively[9]. This lower risk may be explained due to successful CRC surveillance programs and better control of mucosal inflammation from early disease stages[10]. The more recent 40-year surveillance experience in the United Kingdom demonstrated decreasing rates of advanced CRC and interval CRC with cumulative incidences of 0.1%, 6.7%, and 10% in the first, third, and fourth decade after diagnosis, respectively[11]. The reasons for decreasing incidences are thought to reflect effective surveillance, access to surgery, and more effective therapies.

Endoscopic surveillance is the primary recommended CRC prevention strategy, with an active search of early-stage cancer or pre-cancerous (dysplastic) lesions[12]. Endoscopic surveillance has been previously suggested to start 8-10 years after IBD diagnosis based on a historical analysis by Eaden *et al* that showed a CRC risk of 2% 10 years after diagnosis[7]. However, earlier surveillance starting 8 years after diagnosis is modeled to capture an additional 6% of patients developing CRC[13], so newer guidelines embrace this earlier starting time, which may also reflect the emergence of earlier age colorectal cancers described in the population.

Historically, CRC surveillance in patients with IBD has been characterized by extensive four-quadrant non-targeted (random) biopsies to improve the detection of dysplastic mucosa. However, a newer technology that enhances digital mucosal images as high-definition white-light endoscopy (HD-WLE) and dye-assisted chromoendoscopy (CE) with magnification have improved the visualization and detection of early neoplastic lesions, and therefore have increased the diagnostic yield for dysplasia[14,15].

CRC PATHOGENESIS IN IBD

Although the pathogenesis of IBD-related CRC is believed to be different from the pathogenesis of sporadic CRC and CRC that is associated with polyposis and non-polyposis hereditary syndromes, their molecular pathways are similar[16], involving DNA methylation, microsatellite instability, aneuploidy, activation of oncogene Kras, alteration of COX-2 enzymes, and mutation of tumour suppressor genes, with loss of p53 function[17]. One well-known molecular link between cancer and inflammation is the nuclear factor Kappa B (NF-kB)[18]. It can be activated by pro-inflammatory cytokines like interleukin-1 (IL-1), IL-6, and tumor necrosis factor α(TNF-α), ultimately producing reactive oxygen species damaging the DNA and favoring tumor development[19] in Figure 1.

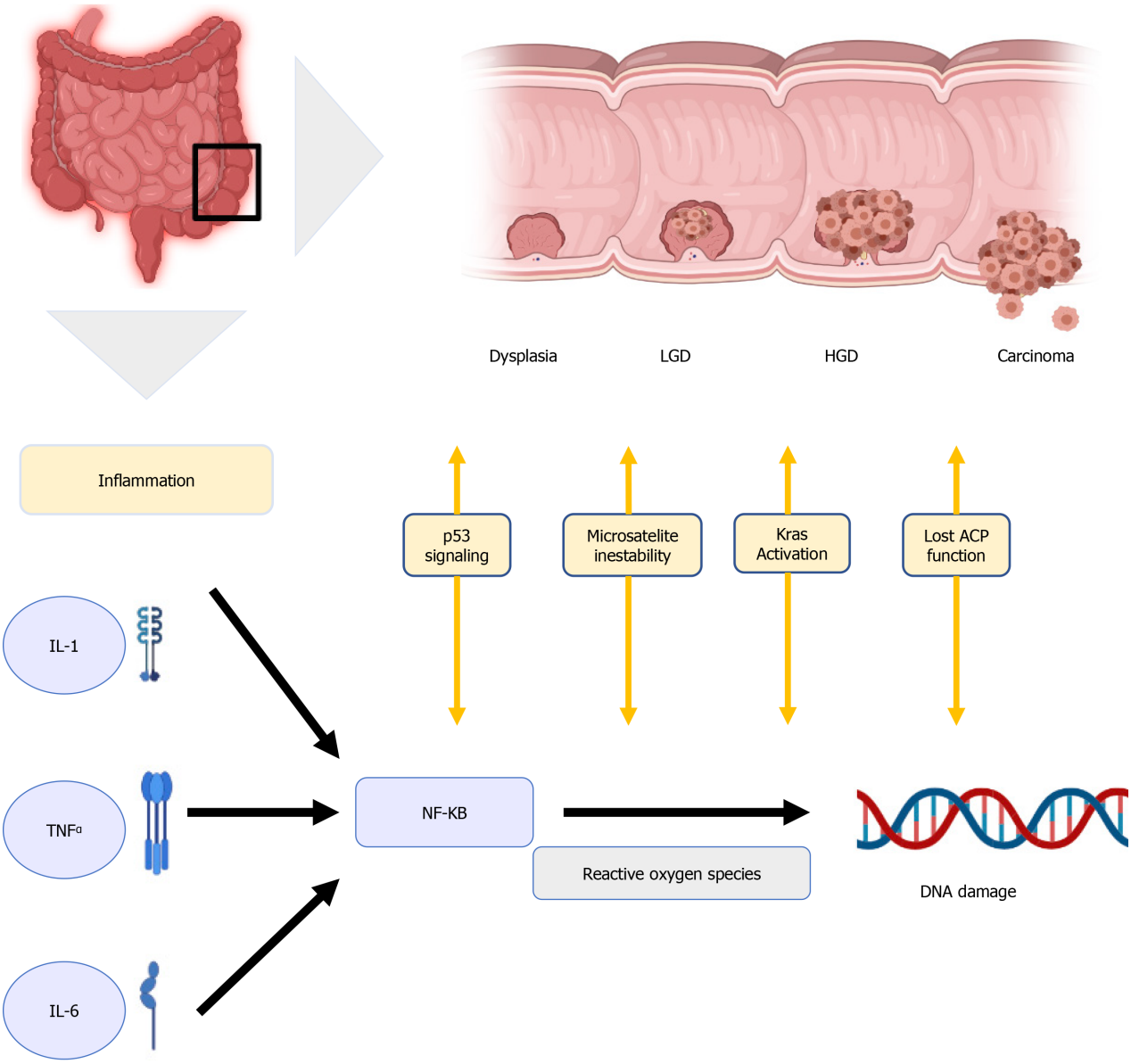

Figure 1 Physiological mechanism. IBD: Inflammatory bowel disease; LGD: Low-grade dysplasia; HGD: High-grade dysplasia.

Inflammation plays a central role in carcinogenesis; as a consequence, the severity of flare-ups with accumulated inflammatory damage (persistence of inflammation) predisposes to the development of CCR. Choi *et al* observed that the accumulative inflammatory burden had a 2-fold increase in the risk of CCR, (95%CI: 1.5 to 2.9; $P <$ 0.001 for endoscopic and 95%CI: 1.4 to 3.0; $P < 0.001$ for histological) for every 10 years of mild, 5 years of moderate o 3.3 years of severe activity disease[20]. The importance of this finding is that it is based not only on the most recent colonoscopy but also on several colonoscopies in a given time to assess the cumulative effect of inflammation. This persistent inflammation mechanism would explain the predominance of right-sided neoplasia that has been described in PSC patients. In a recent study, UC PSC patients who remain in clinical remission have greater endoscopic and histological activity in the right colon compared to UC patients without PSC[21].

Moreover, chronic inflammation may lead to the development of dysplastic changes in colonic mucosa. These changes can be classified as low-grade dysplasia (LGD), high-grade dysplasia (HGD), or indefinite for dysplasia[22]. LGD is characterized by hyperchromatic enlarged nuclei with preserved cell polarity, decreased mucinous differentiation, and dystrophic goblet cells[23,24]. In contrast, HGD presents as atypical cells with prominent nuclear pleomorphism, hyperchromatic stratified nuclei, and loss of cell polarity, and whenever pathologists cannot distinguish between inflammatory-associated and dysplastic changes, the sample is defined as indefinite for dysplasia[23,24]. This should be distinguished from indeterminate findings, which

are usually due to the presence of confounding amounts of histologic inflammation. Given the high inter-observer variability in grading dysplastic changes, guidelines recommend that all cases of suspected dysplasia should be evaluated by two expert pathologists[25,26].

Neoplastic progression can occur multifocally so that dysplasia can be associated with an increased risk of synchronous (simultaneous) or metachronous (six months after diagnosis) dysplasia or carcinoma[25,27].

RISK FACTORS FOR DYSPLASIA AND CRC

Most relevant CRC risk factors in IBD include longer disease duration, greater disease extent (extensive-pancolitis) and degree of inflammation over time[28,29], family history of CRC[30], personal history of dysplasia or colonic stricture, and diagnosis of primary sclerosing cholangitis (PSC) Table 1[31,32].

Younger age at diagnosis and disease duration have been shown as risk factors for CRC in IBD patients, possibly related to more aggressive phenotypes and longer exposure to mucosal inflammation[33]. A previous meta-analysis showed that patients diagnosed before the age of 30 had a CRC standardized incidence ratio (SIR) of 8.2 (95%CI: 1.8-14.6, I2 82%) compared to patients diagnosed after 30-years-old with an SIR of 1.8 (95%CI: 0.9-2.7, I2 81%)[34]. Also, disease extension in UC has been related to a higher risk of CRC, with SIR of 6.9 (95%CI: 1.9-11.9, I2 84%) for extensive colitis and only 1.7 (CI 95% 0.6-4.5 I2 47%) for left-sided colitis; furthermore, in patients with segmental colitis in CD, there was no higher risk of CRC, with a SIR of 1.7 (95%CI: 0.9-2.6, I2 0%)[35]. There is evidence that IBD patients with a prior family history of CRC have at least a two-fold higher risk of IBD-related CRC (adjusted RR = 2.5; 95%CI: 1.4-4.4); moreover, when CRC family history is associated to first-degree relatives, diagnosed under the age of 50, the risk is even higher (RR = 9.2; 95%CI: 3.7-23)[25,35]. There are some cases of Lynch Syndrome with IBD who develop CRC at a younger age, which are more accelerated and significantly compare with patients without IBD. In this scenario, a colectomy would be necessary due to the high risk of recurrence and multiple CRC[36]. This risk has been seen in UC, and only a few cases in CD, so it does not allow conclusions to be drawn about the risk of CRC[37].

The presence of prior dysplasia or stricture is also associated with an increased risk of neoplasia in IBD[38,39]. Furthermore, colonic strictures in any setting should be considered malignant until proven otherwise.[40] Previous studies have reported variable risk of dysplasia or CRC associated with colonic strictures in UC (from 0% to 86%)[41,42] and there is insufficient data for this risk in CD[43]. Regarding the presence of inflammatory polyps, it is debated if they are related to the development of dysplasia. Historically, case-control studies have reported that patients with inflammatory polyps have 1.9-to-2.5-fold increased risk of CRC[29,44], but recent retrospective cohort studies have suggested that they do not independently predict the development of CRC, nor do they predict progression from LGD to HGD or CRC[20,45].

One major risk factor for CRC in IBD is the presence of concomitant PSC. A previous meta-analysis by Soetikno *et al*[46] showed that patients with PSC and UC had a higher risk for development of CRC [odds ratio (OR) of 4.09 (95%CI: 2.89-5.76)]. An observational longitudinal cohort study also reported an increased risk for CRC in patients with PSC and UC compared to patients with UC and no PSC with a SIR of 9.8 (95%CI: 1.9-96.6)[47]. Additionally, patients who are in clinical remission have a higher chance of endoscopic and histological inflammation in the right colon compared to UC patients without PSC, being the place where the CCR is most frequently found[21] in Figure 2.

CRC SURVEILLANCE IN IBD

Recommendations for CRC surveillance in IBD vary according to the type of IBD, comorbidities, and previous family history of CRC. According to the current SCENIC consensus statements and ACG guidelines, surveillance colonoscopies should start 8 years after diagnosis in patients with left-sided or extensive UC, and in patients with a colonic CD that comprise more than 30% of the colonic surface or > 1 colonic segment [48,49]. Patients with a first-degree family history of CRC should start surveillance colonoscopies 10 years before the age their relative was diagnosed with CRC or 8 years after IBD diagnosis, whichever occurs first[50]. In patients with IBD and PSC,

Table 1 Risk factors

Clinical risk factors	Endoscopic risk factors
Disease duration, extension, and severity	Active disease
Personal history of dysplasia	Colonic stricture
Primary sclerosing cholangitis	Pseudopolys (post-inflammatory polyps)
Family history of CRC /dysplasia	Tubular appearance of colon

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn disease.

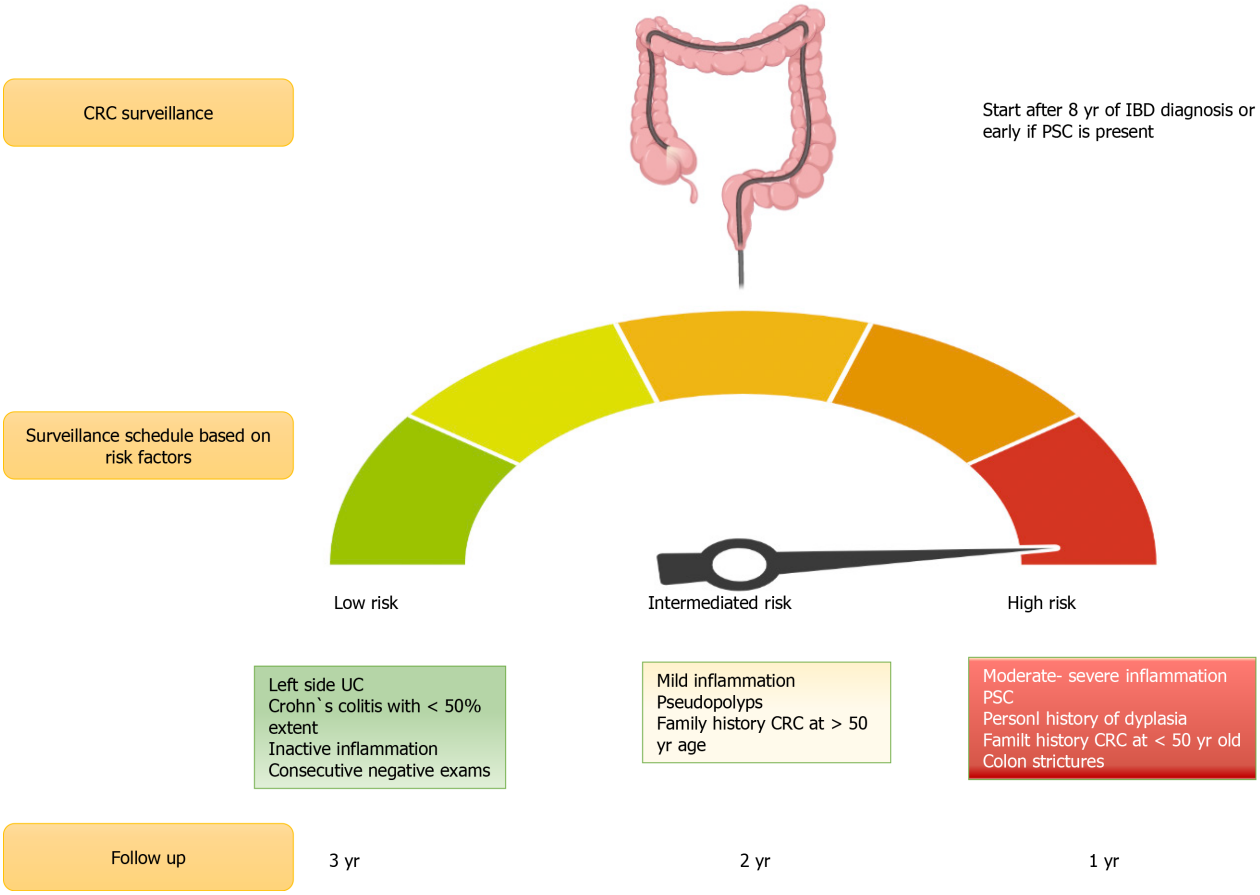

Figure 2 Colorectal cancer risk. CRC: Colorectal cancer; UC: Ulcerative colitis; CD: Crohn disease; PSC: Primary sclerosing cholangitis.

surveillance colonoscopies should start at diagnosis and be repeated on an annual basis[51]. Surveillance colonoscopy intervals are every 1-3 years, according to each patient risk-stratification[27,52]. Patients with isolated proctitis do not need surveillance colonoscopies[51].

ENDOSCOPIC TECHNIQUES FOR DETECTION OF DYSPLASIA

Despite the greater surveillance efforts for early detection of CRC in IBD patients, CRC risk remains significant, and the incidence of interval cases may be due to rapid progression and unclear pathogenesis[53]. In order to perform an optimal evaluation of the colonic mucosa, optimum bowel preparation is essential[54,55].

Several advanced imaging techniques have been developed to improve visualization of mucosal defects, enhancing dysplasia and early CRC detection. High-definition white light endoscopy (HD-WLE) has demonstrated higher adenoma detection than standard definition colonoscopy in patients undergoing screening colonoscopy in non-IBD patients[56]. Chromoendoscopy uses optical or computer/bas

-ed techniques to enhance mucosal details in order to improve lesion detection and characterization[57,58]. This technique can be assisted by different dye agents applied as sprays during colonoscopy, which can be classified as contrast agents (i.e., indigo carmine)[59], absorptive agents (i.e., methylene blue), and reactive staining agents (i.e., Congo red); being the first two, the most commonly used[60]. Among dye-less chromoendoscopy, there are different optical CE techniques. Narrow-band imaging (NBI) is a type of optical CE, based in the use of blue-light technology improving characterization of detected lesions, but has shown no further benefit in primary detection of dysplasia when compared to HD-WLE[61]. Unlike NBI, other dye-less CE methods, such as flexible spectral imaging color enhancement (FICE), visualizes mucosal structures without using optical filters but capturing mucosal imaging and performing digital software-based processing of the captured images. The adequate examination requires a clean mucosa, as stools and blood can obscure interpretation of the images. DCE was more effective in identifying dysplasia compared to white light endoscopy (WLE), but without reaching significant differences compared to HD WLE [62]. Recently, a retrospective analysis also showed no differences in the detection of dysplasia with these techniques, but longer examination time using DCE (24.6 min *vs* 15.4, $P < 0.001$)[63].

The National Institute for Health and Care Excellence (NICE) and the European Crohn's and Colitis Organization (ECCO) have recommended the routine use of CE with targeted biopsies in IBD-CRC surveillance in their society guidelines[49]. In 2015 an international expert consensus, SCENIC (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus) recommended a surveillance study with high-definition colonoscopy or else the use of dye spray chromoendoscopy if a standard definition white-light exam is performed[20]. Prior to HD- WLE, the standard of care for CRC surveillance included four-quadrant non-targeted (random) biopsies every 10 cm from the cecum to the rectum, with a minimum of 32 biopsies, with the goal of detecting "invisible" dysplasia[64]. This technique intended to sample the mucosa in order to identify "invisible" lesions; we now understand that newer imaging technology, if used by experienced endoscopists, has likely made this approach unnecessary in many patients[65].

Virtual chromoendoscopy (VCE) is an optical imaging technique that uses filters to enhance the contrast of both the mucosa and the superficial vasculature, allowing a better evaluation. In a multicenter study with UC patients comparing DCE *vs* NBI, no significant difference was reported between these techniques in detecting neoplastic lesions (OR: 1.02 (95%CI: 0.44-2.35, $P = 0.964$)[66]. A recent randomized controlled trial comparing DCE, VCE, and HD-WLE found that both techniques were non-inferior to DCE[67]. The 2019 ACG guidelines recommend the use of DCE or NBI for the surveillance of dysplasia (conditional recommendation, low quality of evidence)[50].

Despite their low yield, random biopsies may have a role when performed in association with CE in IBD patients with a personal history of neoplasia, an appearing tubular colon, or concomitant PSC. A French multicenter study performed quadrantic random biopsies every 10 cm in patients with a personal history of neoplasia, showing that 12.8% of neoplasia can be detected[68]. Saravia *et al*[69] consider that random biopsies should be performed when CE is not available or when WLE is used in the presence of inflammation or high-risk factors.

NEW TECHNOLOGIES IN CRC DETECTION

Artificial intelligence (AI) is evolving as a topic of interest in the field of gastrointestinal endoscopy. AI has been used in endoscopic polyp detection; no studies on AI in IBD surveillance have been published so far[70].

MANAGEMENT OF DYSPLASIA

It is important to distinguishing polypoid from non-polypoid lesions, due to their different management, prognosis, and follow-up[71]. A meta-analysis performed by Wanders *et al* showed that patients with polypoid lesions had a lower incidence of CRC compared to patients with non-polypoid lesions, which was attributed to the complete endoscopic resection of the first type of lesions[72].

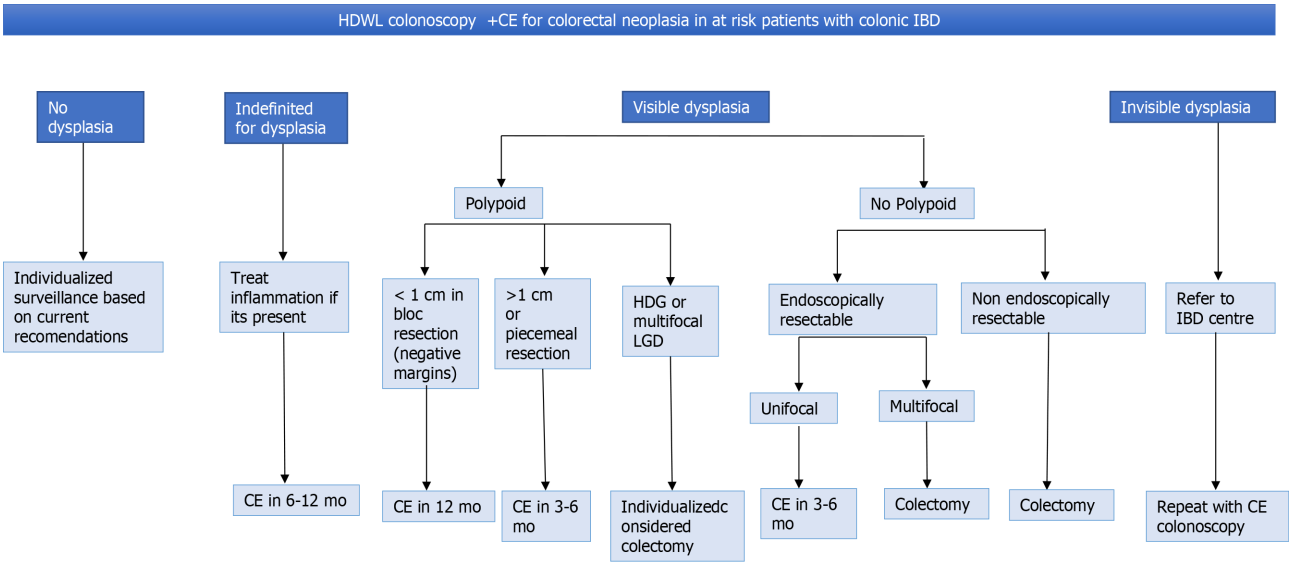

Figure 3 Algorithm for the management of dysplasia. Review all dysplasia with 2 experienced GI pathology. LDG: Low-grade dysplasia; HGD: High-grade dysplasia.

Less than 1 cm polypoid lesions (with negative margins) should be followed up with colonoscopy at 12 mo. For lesions greater than 1 cm or lesions that have been removed piecemeal, surveillance colonoscopy should be performed within 3-6 mo[49]. LGD had a low risk of progression to HGD or CRC from an incomplete resection if it is unifocal. In contrast, multifocal LGD carries substantial risk[73]. The rate of progression from LGD *vs* HGD to adenocarcinoma was significantly greater for HGD ($P < 0.001$)[74]. Although most dysplasias were found in the right colon, being higher in UC, the rate of progression of LGD and HGD dysplasia or adenocarcinoma was not significantly different in CD *vs* UC[75]. A Dutch nationwide cohort study observed that the cumulative incidence of advanced neoplasia was 21.7% after 15 years of follow-up. Male sex, older age at LDG (> 55 years), and follow-up by a tertiary IBD referral center were independent risk factors for advanced neoplasia[76]. The management of HGD in a visible lesion with complete resection is controversial. The decision should be made case by case between colectomy *vs* shorter follow-up[77].

In cases of non-polypoid dysplasia, classically, these were sent to colectomy. However, if there is complete resection, it can be followed up instead of colectomy but, always evaluating progression factors[78].

For endoscopically invisible LGD (found only on random biopsy), it should be referred to an IBD Centre or endoscopist with experience at high-risk surveillance. Surveillance endoscopy using CE with HD-WLE is required in an attempt to identify the neoplastic lesion (or others) and to remove it endoscopically[79]. In Figure 3, the management of dysplasia/LGD and HGD is summarized.

CONCLUSION

It is essential to know which risk factors affect the CRC risk in every IBD patient, allowing to identify the subgroups of patients who need closer surveillance and more intensive treatment. The risk of CRC is increased in IBD but not as high as previously reported. The expanding medical options in IBD have substantially improved our ability to control severe inflammation and likely to reduce the risk of CRC. The advance of new technologies allows us a better characterization of lesions and treat them on time.

Prospective studies to monitor the rate of interval cancer, the cost-effectiveness of surveillance programs are needed.

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ORIGINAL ARTICLE

Retrospective Study

Texture and color enhancement imaging in magnifying endoscopic evaluation of colorectal adenomas

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Abstract

BACKGROUND

Olympus Corporation has developed texture and color enhancement imaging (TXI) as a novel image-enhancing endoscopic technique.

AIM

To investigate the effectiveness of TXI in identifying colorectal adenomas using magnifying observation.

METHODS

Colorectal adenomas were observed by magnified endoscopy using white light imaging (WLI), TXI, narrow band imaging (NBI), and chromoendoscopy (CE). This study adopted mode 1 of TXI. Adenomas were confirmed by histological examination. TXI visibility was compared with the visibility of WLI, NBI, and CE for tumor margin, and vessel and surface patterns of the Japan NBI expert team (JNET) classification. Three expert endoscopists and three non-expert endoscopists evaluated the visibility scores, which were classified as 1, 2, 3, and 4.

RESULTS

Sixty-one consecutive adenomas were evaluated. The visibility score for tumor margin of TXI (3.47 ± 0.79) was significantly higher than that of WLI (2.86 ± 1.02, $P < 0.001$), but lower than that of NBI (3.76 ± 0.52, $P < 0.001$), regardless of the

endoscopist's expertise. TXI (3.05 ± 0.79) had a higher visibility score for the vessel pattern of JNET classification than WLI (2.17 ± 0.90, $P < 0.001$) and CE (2.47 ± 0.87, $P < 0.001$), but lower visibility score than NBI (3.79 ± 0.47, $P < 0.001$), regardless of the experience of endoscopists. For the visibility score for the surface pattern of JNET classification, TXI (2.89 ± 0.85) was superior to WLI (1.95 ± 0.79, $P < 0.01$) and CE (2.75 ± 0.90, $P = 0.002$), but inferior to NBI (3.67 ± 0.55, $P < 0.001$).

CONCLUSION

TXI provided higher visibility than WLI, lower than NBI, and comparable to or higher than CE in the magnified observation of colorectal adenomas.

Key Words: Texture and color enhancement imaging; Adenoma; Colonoscopy; Narrow band imaging; Japan NBI Expert Team; Olympus

Core Tip: Texture and color enhancement imaging (TXI) has been developed as a novel image-enhancing endoscopy. Colorectal adenomas were observed by magnified endoscopy using white light imaging (WLI), TXI, narrow band imaging (NBI), and chromoendoscopy (CE). TXI visibility was compared with the visibility of WLI, NBI, and CE for tumor margin, and vessel and surface patterns of the Japan NBI Expert Team (JNET) classification. TXI provided higher visibility than WLI and lower than NBI for tumor margin. TXI showed higher visibility than WLI and CE, and lower than NBI for the vessel and surface patterns of the JNET classification.

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INTRODUCTION

Colorectal adenomas are precursors to colorectal cancer and their removal prevents occurrence of cancer in this region. Endoscopists with higher adenoma detection rates have lower colorectal cancer incidence and mortality in their patients than those with lower adenoma detection rates[1,2]. Currently, adenomas are a common finding. Hilsden *et al*[3] reported the following benchmarks of adenoma detection rates: minimally acceptable, 25%; standard of care, 30%; and aspirational, 39%. It is recommended that the endoscopists overcome the "minimally acceptable" threshold[3,4]. Therefore, accurate diagnosis of colorectal adenomas is crucial in clinical practice[5-7].

Recent advances in endoscopic technology have improved the accuracy of endoscopy using image-enhanced endoscopy (IEE) for lesions that are difficult to observe using conventional white light imaging (WLI). Since narrow band imaging (NBI) was developed as an IEE modality, evidence on the usefulness of IEE has been accumulated and IEE is commonly used in daily practice. NBI selects blue and green wavelengths using optical filters with the elimination of red light, thus emphasizing mucosal surface structures and blood vessels[8]. NBI has been reported to be effective in detecting[9] and characterizing lesions[10-12]. Following NBI, blue light imaging (BLI) and linked color imaging (LCI) have become available as new IEE modalities. BLI and LCI irradiate mucosa with a short wavelength, narrow-band light, which includes light amplification by stimulated emission of radiation or light emitting diode, without an optical filter. Furthermore, the acquired color information is reallocated to different colors that are similar to the mucosal color, resulting in improved performance in depicting blood vessels. In addition, image processing that enhances color separation for red color permits clear visualization of red blood vessels and white pits in LCI[13]. The efficacy of BLI and LCI has also been extensively

(approval no. RKK227).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. For full disclosure, the details of the study are published on the home page of Toyoshima Endoscopy Clinic.

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reported[14]. Texture and color enhancement imaging (TXI), which is a novel method to enhance images, was developed in the new endoscopy system EVIS X1 (Olympus Corporation, Tokyo, Japan) in 2020.

TXI is designed to enhance three image factors, including texture, brightness, and color, in WLI to clearly define subtle tissue differences by applying the retinex theory [15,16]. Retinex is based on the theory of "color constancy" and "brightness constancy", in which the human eye can perceive color and brightness regardless of the illumination light. TXI consists of the following six processes. First, the input image is split into two layers, base and detail. Next, the brightness in the dark regions of the base layer is adjusted. Tone-mapping is applied to the corrected base layer in step three. Fourth, texture enhancement is applied to the detail layer to enhance the subtle contrast. In step five, the base layer after tone-mapping and the detail layer after texture enhancement are recombined. A TXI image produced in the fifth step is immediately displayed in TXI mode 2. In the final step, color enhancement is applied to the output of TXI mode 1 to more clearly define the slight color contrast. The color enhancement algorithm of TXI was designed to expand the color difference between red and white hues in the image[16].

The Japan NBI Expert Team (JNET) classification is a standard for diagnosing the histology of a neoplasm by observing the surface structure (vessel pattern and surface pattern) of the neoplasm using magnified NBI. The JNET classification is widely used in clinical practice for the diagnosis of adenoma. It has proven to be useful for the diagnosis of superficial colorectal neoplasms in a clinical setting by both expert and non-expert endoscopists[12]. A meta-analysis suggested that the diagnostic efficacy of the JNET classification may be equivalent to that of the Pit pattern classification[17]. Furthermore, the algorithm for the treatment of colorectal polyps using the JNET classification was reported to be valid[18]. Meanwhile, evidence supports that chromoendoscopy (CE) increases colorectal polyp detection and contributes to accurate polyp diagnosis[6,19-22].

Currently, the only clinical studies on TXI that have already been published are those by Ishikawa *et al*[23] and Abe *et al*[24], wherein TXI was used for imaging the stomach. Some clinical trials on the efficacy of TXI in colorectal polyp observation are ongoing; however, no published reports on colonoscopy are available in PubMed or the Cochrane Library. Therefore, the aim of this study was to investigate the effectiveness of TXI for colorectal adenomas. The visibility of TXI was compared with the visibility of WLI, NBI, and CE for the tumor margin and JNET classification pattern using magnifying observation.

MATERIALS AND METHODS

Patients

Patients who underwent colonoscopy at Toyoshima Endoscopy Clinic (Tokyo, Japan), which is a representative clinic in Japan, from April to May 2021, were enrolled. Patients with removed adenomas were eligible for the study. When patients had multiple adenomas, they were treated individually. Adenomas were diagnosed histopathologically. Indications for colonoscopy included screening, examination of symptoms, investigation for a positive fecal immunochemical test, and polyp surveillance. Patients with inflammatory bowel disease were excluded.

Ethics

This study was conducted in accordance with the ethical guidelines for medical studies in Japan. Written informed consent was obtained from the patients at the time of colonoscopy to use their data for research purposes. The study design was described in a protocol prepared by Toyoshima Endoscopy Clinic and was approved by the Certificated Review Board, Yoyogi Mental Clinic on July 16, 2021 (approval No. RKK227). We published this study's protocol on our institute's website (http://www.ichou.com) so that patients could opt out of the study if they did not wish to participate. All clinical investigations were conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Endoscopy

EVIS X1 video system center (CV-1500), 4 K resolution ultra-high-definition liquid crystal display monitor (OEV321UH), and colonoscope CF-HQ290Z (Olympus Corporation, Tokyo, Japan) were used in this study setting. TXI has two methods, namely modes 1 and 2, and the enhancement of brightness and texture is similar

between them. Because the enhancement of the color contrast of mode 1 is superior to that of mode 2[16], this study adopted mode 1. For the enhanced structure level, A8 was selected for WLI, NBI, and CE. The type A mode is ideal for observation of larger mucosal tissues with high contrast, whereas the type B mode is suitable for observation of vascular tissues. There are eight levels among the type A mode, of which A8 is the most emphasized, and A1 is the least emphasized mode. A 0.05% indigo carmine was used for the CE. The T-File System (STS-Medic Inc., Tokyo, Japan) was used to file the endoscopic images and document the endoscopic findings.

One expert endoscopist performed colonoscopy and magnified observation using the WLI, TXI, NBI, and CE modalities. Lesions were first washed carefully with water to remove the mucus and dye from the mucosal surface; then, images were obtained through WL, TXI, and NBI. The lesions were subsequently stained for CE. The endoscopist took an image within 15 s for each modality.

Visibility scoring

We investigated the visibility of the tumor margin, and the vessel and surface patterns according to the JNET classification. The vessel pattern shows the pattern of superficial microvessels, which appear red in WLI, TXI, and CE, and brown in NBI. The surface pattern indicates the pattern of superficial crypts, which appear whitish in all modalities. JNET type 2A corresponds to the histopathological classification of low-grade intramucosal neoplasia, including adenoma. The vessel pattern of type 2A is of a regular caliber and distribution (meshed and/or spiral pattern). The surface pattern of type 2A is defined as regular (tubular, branched, and/or papillary)[10-12].

As in previous reports, the visibility score was defined as follows: score 4, excellent (easily detectable); score 3, good (detectable with careful observation); score 2, fair (hardly detectable without careful examination); score 1, poor (not detectable without repeated careful examination)[12,14]. Representative images of each score are shown in Figures 1, 2, and 3.

Three expert endoscopists and three non-expert endoscopists evaluated the visibility score. The images studied were observed without zooming. The endoscopist assessed all images at the same size and magnification. A physician with more than 5000 experiences in colonoscopy was defined as an expert endoscopist and one with less than 5000 experiences was considered a non-expert[12].

Outcomes

The main outcomes of this study were the mean visibility scores for tumor margin, vessel pattern of JNET classification, and surface pattern of JNET classification based on WLI, TXI, NBI, and CE observations. We collected data on age and sex of the patients, the location of adenomas, size of adenomas, morphology of adenomas based on the Paris endoscopic classification of neoplastic lesions[25], histological subtype (*i.e.*, tubular or villous) of adenomas, and atypia of adenomas as clinicopathological characteristics.

Statistical analysis

The visibility scores of TXI and other modalities were compared using the Wilcoxon signed-rank test. Statistical significance was defined as a P value less than 0.05. All statistical data were analyzed using the statistical software Ekuseru-Toukei 2015 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

RESULTS

Patients

The clinicopathological characteristics of the 37 consecutive patients with 61 adenomas evaluated in this study are shown in Table 1. The mean age was 59.1 years, and men accounted for 51.4%. Of the adenomas with an average size of 4.2 mm, 78.7% were located on the right side, 86.9% had a flat morphology, and all were tubular subtype with low-grade dysplasia.

Visibility score for tumor margin

The visibility score for the tumor margin of TXI was higher than that of WLI, but lower than that of NBI. Similar tendencies were obtained regardless of the endoscopist's expertise (Table 2).

Table 1 Clinicopathological characteristics of patients and adenomas

Patients, *n*	37
Age, mean (range, SD), yr	59.1 (41-79, 9.0)
Sex, male/female, *n*	19/18
Adenomas, *n*	61
Location,cecum/ascending/transverse/descending/sigmoid/rectum, *n*	5/8/35/3/10/0
Size, mean (range, SD), mm	4.2 (1-12, 2.3)
Morphology[1], Ip/Is/IIa/IIb, *n*	2/6/48/5
Histological subtype, tubular/villous, *n*	61/0
Dysplasia, low-grade/high-grade, *n*	61/0

[1]Morphology was performed according to the Paris endoscopic classification of neoplastic lesions.

Table 2 Visibility scores of tumor margin, vessel pattern of Japan narrow band imaging Expert Team classification, and surface pattern of Japan narrow band imaging Expert Team classification for white light imaging, texture and color enhancement imaging, narrow band imaging, and chromoendoscopy

	WLI	TXI	NBI	CE	WLI *vs* TXI, *P* value	TXI *vs* NBI, *P* value	TXI *vs* CE, *P* value
Tumor margin							
All, mean (SD)	2.86 (1.02)	3.47 (0.79)	3.76 (0.52)	3.52 (0.84)	< 0.001	< 0.001	0.21
Expert, mean (SD)	2.85 (0.96)	3.57 (0.66)	3.81 (0.43)	3.64 (0.70)	< 0.001	< 0.001	0.14
Nonexpert, mean (SD)	2.86 (1.08)	3.37 (0.90)	3.72 (0.59)	3.39 (0.94)	< 0.001	< 0.001	0.73
Vessel pattern							
All, mean (SD)	2.17 (0.90)	3.05 (0.79)	3.79 (0.47)	2.47 (0.87)	< 0.001	< 0.001	< 0.001
Expert, mean (SD)	2.31 (0.87)	3.24 (0.67)	3.80 (0.41)	2.57 (0.85)	< 0.001	< 0.001	< 0.001
Nonexpert, mean (SD)	2.03 (0.90)	2.86 (0.85)	3.78 (0.52)	2.37 (0.88)	< 0.001	< 0.001	< 0.001
Surface pattern							
All, mean (SD)	1.95 (0.79)	2.89 (0.85)	3.67 (0.55)	2.75 (0.90)	< 0.001	< 0.001	0.002
Expert, mean (SD)	1.92 (0.74)	2.96 (0.78)	3.70 (0.47)	2.67 (0.81)	< 0.001	< 0.001	< 0.001
Nonexpert, mean (SD)	1.97 (0.83)	2.83 (0.92)	3.64 (0.61)	2.83 (0.97)	< 0.001	< 0.001	0.94

The visibility score was defined as follows: score 4, excellent (easily detectable); score 3, good (detectable with careful observation); score 2, fair (hardly detectable without careful examination); score 1, poor (not detectable without repeated careful examination). NBI: Narrow band imaging; JNET: Japan NBI Expert Team; WLI: White light imaging; TXI: Texture and color enhancement imaging; CE: Chromoendoscopy.

Visibility score for vessel pattern of JNET classification

TXI had a higher visibility score for vessel pattern of JNET classification than WLI and CE, but lower visibility score than NBI. Similar tendencies were observed regardless of the endoscopist's experience (Table 2).

Visibility score for surface pattern of JNET classification

The visibility score of TXI for surface pattern of JNET classification was higher than those of WLI or CE, but lower than that of NBI. However, no difference was observed in the visibility scores between TXI and CE for non-expert endoscopists (Table 2).

DISCUSSION

This study showed that TXI provided higher visibility than WLI, but lower visibility

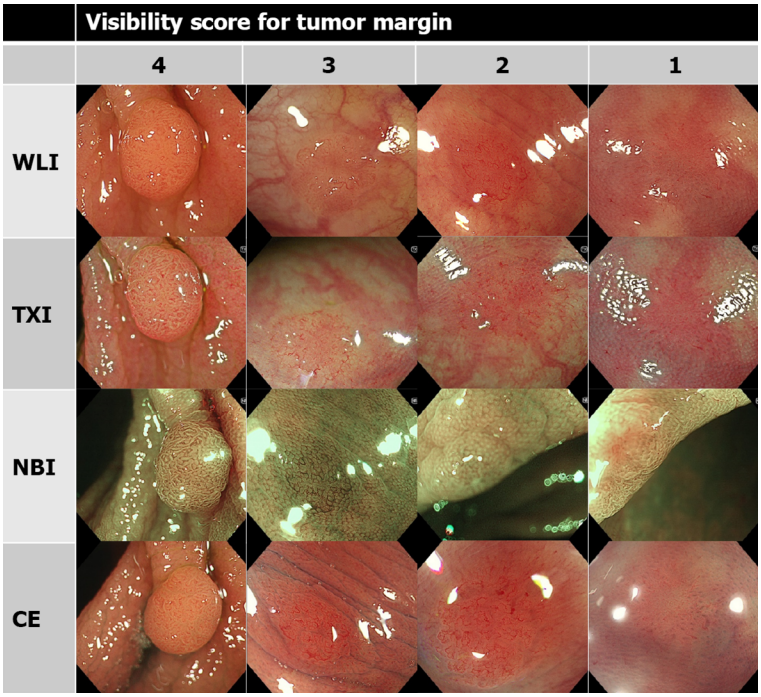

Figure 1 Representative images of visibility score for tumor margin. Visibility score was defined as following: score 4, excellent (easily detectable); score 3, good (detectable with careful observation); score 2, fair (hardly detectable without careful examination); score 1, poor (not detectable without repeated careful examination). WLI: White light imaging; TXI: Texture and color enhancement imaging; NBI: Narrow band imaging; CE: Chromoendoscopy.

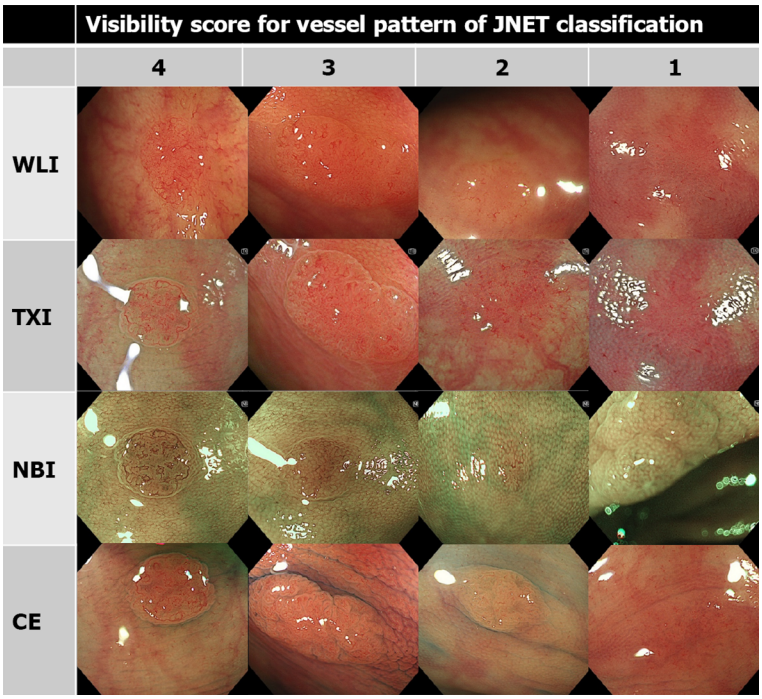

Figure 2 Representative images of visibility score for vessel pattern of Japan narrow band imaging Expert Team classification. Visibility score was defined as following: score 4, excellent (easily detectable); score 3, good (detectable with careful observation); score 2, fair (hardly detectable without careful examination); score 1, poor (not detectable without repeated careful examination). NBI: Narrow band imaging; JNET: Japan NBI Expert Team; WLI: White light imaging; TXI: Texture and color enhancement imaging; CE: Chromoendoscopy.

than NBI for margin and surface structure (*i.e.*, JNET patterns) of adenoma. Moreover, TXI had superior visibility for the surface structure of adenoma to CE. TXI is designed to enhance the three image components (*i.e.*, texture, brightness, and color) of WLI because it clearly defines subtle tissue differences and minimizes gross changes that negatively impact familiarity.

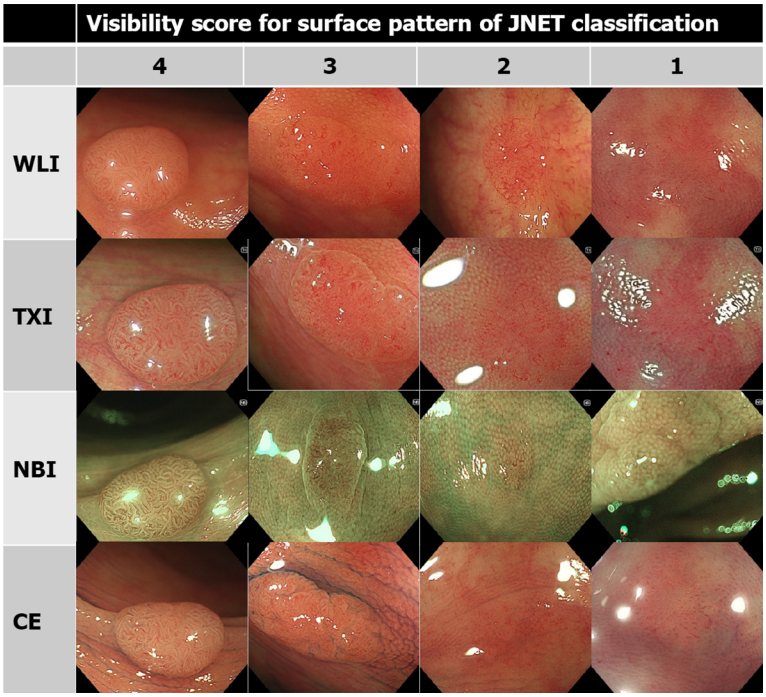

Figure 3 Representative images of visibility score for surface pattern of Japan narrow band imaging Expert Team classification. Visibility score was defined as following: score 4, excellent (easily detectable); score 3, good (detectable with careful observation); score 2, fair (hardly detectable without careful examination); score 1, poor (not detectable without repeated careful examination). NBI: Narrow band imaging; JNET: Japan NBI Expert Team; WLI: White light imaging; TXI: Texture and color enhancement imaging; CE: Chromoendoscopy.

Although TXI was inferior to NBI in a detailed observation of the lesions, many endoscopists prefer to maintain consistency regarding the brightness and color in the original WLI because WLI is used as the standard practice for observation of the entire mucosa. As shown in this study, TXI may improve the balance of image features vital to an endoscopist searching for abnormalities, with texture enhancement, color enhancement, and selectively increased brightness.

Olympus Corporation first developed the NBI in 2007. Fujifilm Corporation developed a similar BLI product. NBI uses ambient light with wavelengths of 415 nm and 540 nm, whereas BLI uses wavelengths of 410 and 450 nm. The images of NBI and BLI are similar. The diagnostic performances of NBI and BLI were also similar for colorectal and esophageal lesions[26]. Fujifilm Corporation developed the LCI. A randomized controlled trial showed that LCI was significantly superior to standard WLI colonoscopy for polyp detection[13]. Currently, LCI-based observations are becoming mainstream. However, Olympus did not have a mode corresponding to that of LCI until recently. Recently, Olympus released TXI as a mode similar to that of LCI.

Although LCI and TXI have similar images, there are several differences in their principles. LCI uses the same illumination as BLI-bright, the images are converted to resemble those of WLI, and color is enhanced such that red is changed to vivid red and white to clear white. On the other hand, TXI uses white light, brightness is adjusted, and texture and color are enhanced. In this study, TXI showed improved tumor margin visibility than WLI. Similar to LCI, TXI may contribute to the improvement in adenoma detection rate; however, future studies are warranted.

In this study, the magnified TXI was inferior to the magnified NBI. Several reports have shown that magnified LCI with CE is superior to magnified BLI. Sakamoto *et al* [27] reported that magnified LCI with crystal violet staining provided more diagnostic information than magnified BLI and WLI. Kitagawa *et al*[28] reported that magnified LCI with indigo carmine was superior to magnified BLI. Magnified TXI with CE needs to be further investigated in future studies.

Strengths and limitations

The strength of this study is that it is the first report on the efficacy of TXI in colonoscopy. Second, this study targeted colorectal adenomas, which are common in daily practice; however, evaluation of visibility of malignant tumors is required. Artificial intelligence (AI) has made remarkable progress in the field of endoscopy [29], and we have shown the possible usefulness of TXI for AI endoscopy in the future.

The present study has some limitations. This was a single-center, retrospective study. However, since our institution specializes in endoscopy, the endoscopic environment is well managed. Multicenter randomized control trials are required in the future. Since this study is only for magnified observation, it is desirable to study non-magnified observations as well. TXI has two modes: mode 1 and mode 2. Mode 2 includes brightness adjustment and texture enhancement, and mode 1 adds color enhancement to mode 2. Mode 2 is more natural than mode 1. Since TXI mode 1 was shown to be superior to TXI mode 2 in visibility for gastric neoplasms[23], only mode 1 was investigated in this study. However, comparative studies of visibility between modes 1 and 2 in colonoscopy should be conducted in the future. Additionally, since this study only used CF-HQ290Z, evaluation in various other scopes is necessary. Finally, colorectal adenomas that we investigated were as small as 4.2 mm, and most of them were morphologically flat (86.9%) and located in the proximal colon (78.7%), compared with the adenomas in previous Japanese studies[12]. Our previous study showed that an expert endoscopist with a high adenoma detection rate frequently detected diminutive and flat adenomas in the proximal colon[22]. In the present study, one expert endoscopist conducted all colonoscopies; hence, the adenomas investigated cannot be generalized. In the future, studies with a larger number of cases evaluated by non-expert endoscopists are warranted.

CONCLUSION

TXI provided higher visibility than WLI, lower than NBI, and comparable to or higher than CE in the magnified observation of colorectal adenomas. Further accumulation of evidence on the performance of TXI is required in the future.

ARTICLE HIGHLIGHTS

Research background

Olympus Corporation has developed texture and color enhancement imaging (TXI) as a novel image-enhancing endoscopic technique.

Research motivation

There are no reports on the use of TXI in the colon.

Research objectives

To investigated the effectiveness of TXI in identifying colorectal adenomas using magnifying observation.

Research methods

Colorectal adenomas were observed by magnified endoscopy using white light imaging (WLI), TXI, narrow band imaging (NBI), and chromoendoscopy (CE). TXI visibility was compared with the visibility of WLI, NBI, and CE for tumor margin, and vessel and surface patterns of the Japan NBI Expert Team (JNET) classification. The visibility scores were classified as 1, 2, 3, and 4.

Research results

Sixty-one consecutive adenomas were evaluated. The visibility score for tumor margin of TXI was significantly higher than that of WLI, but lower than that of NBI. TXI had a higher visibility score for the vessel pattern of JNET classification than WLI and CE, but lower visibility score than NBI. For the visibility score for the surface pattern of JNET classification, TXI was superior to WLI and CE, but inferior to NBI.

Research conclusions

TXI provided higher visibility than WLI, lower than NBI, and comparable to or higher than CE in the magnified observation of colorectal adenomas.

Research perspectives

TXI may contribute to the improvement in adenoma detection rate. Further accumulation of evidence on the performance of TXI is required in the future.

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MINIREVIEWS

Role of intraluminal brachytherapy in palliation of biliary obstruction in cholangiocarcinoma: A brief review

Divya Khosla, Samreen Zaheer, Rahul Gupta, Renu Madan, Shikha Goyal, Narendra Kumar, Rakesh Kapoor

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Abstract

Surgery is the only curative treatment for cholangiocarcinoma. However, most patients present with advanced disease, and hence are unresectable. Thus, the intent of treatment shifts from curative to palliative in the majority of cases. Biliary drainage with intraluminal brachytherapy is an effective means of relieving the malignant biliary obstruction. In this review, we discuss the role of brachytherapy in the palliation of obstructive symptoms in extrahepatic cholangiocarcinoma.

Key Words: Biliary tract; Cholangiocarcinoma; Extrahepatic; Intraluminal brachytherapy

Core Tip: Intraluminal brachytherapy (ILBT) is an effective means for palliation of biliary obstruction in patients with cholangiocarcinoma. It delivers a high dose of radiation to the tumor but spares surrounding normal tissues, thus avoiding many of the side effects seen with external beam radiation. The high dose *per* fraction in ILBT can have an ablative effect on the tumor and can lead to better symptom control and quality of life. ILBT, when combined with these drainage procedures, improves the stent patency rates by inhibiting tumor ingrowth.

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INTRODUCTION

Biliary tract carcinomas, also known as cholangiocarcinomas, may be intrahepatic or extrahepatic. Intrahepatic cholangiocarcinomas arise from the biliary duct epithelium within the liver parenchyma. Extrahepatic cholangiocarcinomas include hilar and distal cholangiocarcinomas. Among these variants, the hilar variety, also known as Klatskin tumor, is the most common. It arises at the junction of the right and the left hepatic ducts.

The Asian population is more susceptible to developing bile duct carcinomas. The disease is more frequently seen in Thailand, India, Japan, and Korea. The incidence varies from 0.3 to 6 *per* lakh population[1]. Surgery is the only curative treatment. However, the disease is resectable only in a minority of the cases. Biliary obstruction is common and results in symptoms such as jaundice, intense pruritis, or pain abdomen. The various means of palliation include biliary drainage procedures, which may be endoscopic or percutaneous, external beam radiation therapy (EBRT), palliative chemotherapy, and intraluminal brachytherapy (ILBT) with or without EBRT.

CLINICAL FEATURES AND PATHOLOGY

Cholangiocarcinoma is a disease of the elderly, mostly affecting those more than 60 years of age. It is seen more commonly in males as compared to females. The risk factors include parasitic infection by organisms such as *Clonorchis sinensis* and *Opisthorchis viverrini*, biliary stones, and smoking. Primary sclerosing cholangitis and hepatitis C are the other risk factors. Primary sclerosing cholangitis with or without cholangitis is the commonest risk factor in Western countries[2].

In the early stages, the patient is usually asymptomatic. The signs and symptoms are non-specific. These may include pain abdomen, fever, jaundice, loss of weight, loss of appetite, generalized itching, and other features of biliary obstruction. Distant metastasis is fairly common[3]. Most of the patients present with either locally advanced or metastatic disease.

Cholangiocarcinomas are histologically adenocarcinomas in 95% of cases[2]. These can be well-differentiated, moderately differentiated, or poorly differentiated[4].

DIAGNOSTIC WORK-UP

Ultrasonography (USG) is the baseline investigation done whenever a biliary obstruction is suspected. It may reveal dilated biliary channels, any mass, or the presence of gallstones. Contrast-enhanced computed tomography (CECT) is the standard imaging tool, especially for staging and preoperative assessment. The delayed scans are useful for diagnosing intrahepatic cholangiocarcinomas which may show contrast enhancement on delayed scans due to abundant fibrous stroma[5-7]. However, CECT may not show the true longitudinal extent of perihilar cholangiocarcinoma[8]. Magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) is considered the imaging modality of choice. It allows the assessment of the entire biliary tree as well as the vascular anatomy[9].

Cancer antigen (CA) 19-9, carcinoembryonic antigen (CEA), and CA-125 are the non-specific tumor markers, which may help in establishing the diagnosis[10]. Tissue diagnosis is essential before a patient can be given chemotherapy or radiotherapy. This may be quite challenging, especially if the patient has primary sclerosing cholangitis or biliary strictures. The biopsy samples, collected by endoscopic imaging and tissue sampling, are usually inadequate for molecular typing. In this setting, liquid biopsy holds promise. It is mainly based on circulating free DNA and circulating tumour DNA[11]. Cholangiocarciomas exhibit specific RNA profiles in extra-cellular vesicles in a patient's serum and urine. It is one of the promising liquid biopsy markers[12].

MANAGEMENT

Surgery is the only curative treatment for cholangiocarcinomas. The disease is resectable in only 10%-15% of the patients[13,14]. The low resection rates may be due to invasion of the hepatic artery or portal

vein, lymph node involvement, or the invasion of the adjacent structures. Some patients may present with peritoneal or distant metastasis, so are inoperable, and need to be managed with palliative intent. Operative mortality has been reported to be 5%-10% in some studies[14-16]. The 5-year survival rates after surgery are 9%-18% for proximal bile duct lesions and 20%-30% for distal bile duct lesions[2]. Although phase 2 studies and some retrospective studies suggest the advantage of adding adjuvant therapy, there are no phase 3 studies to support this[17-20].

Bonet Beltrán *et al*[21] did a systematic review and meta-analysis in patients with extrahepatic bile duct cancer. The authors reported a significant benefit of adjuvant radiation, especially in patients with extrahepatic cholangiocarcinoma. This benefit was seen in terms of improved overall survival[21].

Sahai *et al*[22] reviewed the literature on the role of radiation in adjuvant, neoadjuvant, definitive, and palliative settings. They concluded that stenting with palliative radiotherapy, either external or brachytherapy, improves the stent patency rates and survival in unresectable cholangiocarcinoma[22].

There is no definite consensus on the role of adjuvant chemotherapy. The studies have reported variable results. A retrospective study on patients with hilar cholangiocarcinoma showed a significant improvement in survival in those who received adjuvant chemotherapy[23]. The greatest benefit of adjuvant chemotherapy is seen in those with lymph node positive or resection margin positive status [24]. After the BILCAP study, capecitabine is considered to be the standard treatment for biliary tract cancers in the adjuvant setting[25].

Neoadjuvant therapy has been explored in cholangiocarcinoma with the aim to achieve negative surgical margins and improve survival rates. Nelson *et al*[26] conducted a study in patients diagnosed with extra-hepatic cholangiocarcinoma. These patients received neoadjuvant chemo-radiotherapy with 5-flourouracil and EBRT with or without brachytherapy. They reported a R0 resection rate of 91.7%[26]. Similar results have been reported by Jung *et al*[27] and Sumiyoshi *et al*[28].

Novel treatment options are opening the doors of a new world. There is increasing interest in the use of targeted therapy and immunotherapy. Targeted therapies have demonstrated a role in mainly intrahepatic cholangiocarcinoma[29]. Fibroblast growth factor receptor (FGFR) aberrations and isocitrate dehydrogenase (IDH) mutations based therapy hold promise[30,31].

There are several ongoing trials on immunotherapy in advanced biliary tract cancers. Although monotherapy with immune check-point inhibitors or their combination with other anti-cancer agents shows only modest survival advantages and efficacy, there is a need to test these patients for deficiency in mismatch repair proteins (dMMR), high microsatellite instability (MSI-H), increased tumor mutational burden (TMB), and programmed death-ligand 1 (PD-L1) expression[32,33].

Due to low resectability, the goal of treatment is palliation in most of the patients. Endoscopic retrograde cholangiopancreaticography (ERCP) or percutaneous transhepatic biliary drainage (PTBD) are the initial procedures that may be used to relieve biliary obstruction resulting from cholangiocarcinoma. These procedures are only palliative with a median survival of around 6 mo[34]. This article provides a concise overview of the role of ILBT in the palliation of biliary obstruction. Biliary drainage, which is done either endoscopically or percutaneously, can palliate symptoms, but ILBT can decrease the tumor size and delay the tumor ingrowth.

ROLE OF BRACHYTHERAPY

ILBT can be used in cholangiocarcinomas with both palliative and curative intent. With curative intent, it can be used following chemoradiotherapy to escalate the tumor dose and thus increase the local control[35]. The main indication in the palliative setting is to relieve the biliary obstruction. The mechanism may be *via* preventing stent re-occlusion, which may occur due to tumor ingrowth[36,37].

When ILBT is combined with EBRT, usually 30-40 Gy are delivered *via* EBRT and 15-20 Gy in 2-3 fractions *via* high dose rate (HDR) brachytherapy. When pulsed dose rate brachytherapy (PDR) is used in the combined modality setting, a single course of 20 Gy is usually prescribed[3]. In the palliative setting, the HDR ILBT dose is usually 15-20 Gy in 3-4 Gy/fraction. When PDR brachytherapy is used, 1 or 2 fractions of 20-40 Gy may be prescribed[3].

ILBT techniques, dose, and response

ILBT can be performed using ERCP or PTBD. Whenever possible, percutaneous transhepatic technique is preferred. It is reported that when PTBD is combined with ILBT, the median survival time increases [38,39]. The feasibility of ILBT is better with PTBD. Lesions in the right and left hepatic duct, as well as the common bile duct, can be easily assessed. Before PTBD, imaging is done to know the exact site and extent of the obstruction. It can be assessed *via* USG, CT, or MRI. First, percutaneous transhepatic cholangiography is performed followed by biliary decompression. ILBT catheters are inserted when serum bilirubin levels decrease and the patient stabilizes. Jain *et al*[40] performed ILBT when the serum bilirubin levels decreased to 2 mg% or fell to 50% of the baseline. Other inclusion criteria reported by them included Eastern Cooperative Oncology Group (ECOG) performance status 0-2; absence of fever, signs of cholangitis, or any evidence of distant metastasis[40]. Aggarwal *et al*[34] did ILBT after biliary drainage *via* PTBD when the serum bilirubin levels were below 5 mg%[34]. They did PTBD under USG

Table 1 Some studies in which brachytherapy has been used with palliative intent

No.	No of patients	Diagnosis	PTBD	EBRT	Dose of ILBT	Survival	Stent patency	Ref.
1	18	Malignant biliary obstruction	Yes	-	16 Gy in 2 fractions	8.27 mo (median survival)	-	Aggarwal *et al* [34]
2	48	Bile duct and pancreatic cancer	Yes	-	25 pulses of 0.8 Gy hourly (total dose of 20 Gy PDR)	11.2 mo for bile duct carcinoma	-	Skowronek *et al*[36]
3	32	Non resectable biliary malignancy	Yes	-	5 Gy in 6 fractions	358 d in Klatskin-tumour	418 d	Bruha *et al*[37]
4	22	Malignant biliary obstruction	Yes	Yes	15-31 Gy (mean 25 Gy)	22.6 mo	19.5 mo	Eschelman *et al* [39]
5	12	Malignant obstructive jaundice	Yes	Yes (6 patients)	10-14 Gy	-	9.8 mo	Jain *et al*[40]
6	34	Malignant obstructive jaundice	Yes	-	14-21 Gy in 3-4 fractions	9.4 mo	12.6 mo	Chen *et al*[43]
7	14	Bile duct cancers	Yes	Yes (5 patients)	10 Gy, 2 fractions of 2.5 Gy 6 h apart for 2 d	6.5 mo (median survival)	-	Mayer *et al*[44]
8	8	Malignant obstruction of bile duct	Yes	-	2 fractions of 10 Gy each	7.5 mo	6.9 mo	Kocak *et al*[45]

PTBD: Percutaneous transhepatic biliary drainage; EBRT: External beam radiation therapy; ILBT: Intraluminal brachytherapy.

and fluoroscopic guidance. After biliary decompression, an internal-external drainage tube was inserted and left in place for 7-10 d to allow bilirubin levels to fall and the patient's general condition to improve. When ILBT was performed, the external–internal catheter was replaced with brachytherapy catheter. Its tip was placed 1.5-2 cm beyond the distal end of the stricture. These patients received a dose of 8 Gy in 2 fractions at an interval of 1 wk *via* HDR brachytherapy. Various brachytherapy doses and schedules are described in the literature. Jain *et al*[40] used a dose of 10-14 Gy at 1 cm from the central axis of the source, which was delivered *via* HDR microselectron[40].

Deufel *et al*[41] have described the HDR brachytherapy in patients with cholangiocarcinoma *via* a nasobiliary route[41]. They did the procedure using an 8.5 Fr or 10 Fr nasobiliary catheter inserted *via* ERCP technique. This was followed by insertion of a 4.7 Fr treatment catheter into the nasobiliary catheter. The dose schedules described are a single fraction of 9.3 Gy or fractionated regime using four fractions of 4 Gy delivered twice a day. For patients who are suitable for liver transplantation after neoadjuvant chemoradiation, the minimally invasive nasobiliary approach may be preferred as there is a higher risk of tumor seeding with transhepatic technique[42]. However, the nasobiliary route is technically more difficult and may not be preferred in the palliative setting.

Bruha *et al*[37] in their study on cholangiocarcinoma patients with malignant obstructive jaundice treated by HDR ILBT, showed that the mean stent patency was 418 d[37]. Jain *et al*[40] reported a mean stent patency duration of 9.4 mo in patients with cholangiocarcinoma treated by PTBD and ILBT[40].

Chen *et al*[43] showed a similar trend in their study. The stent patency rate in patients who underwent ILBT with PTBD was 45%. However, this rate was just 21%in the group of patients who had only stent placement. The dose of ILBT used was 14-21 Gy in 3-4 fractions. The duration of stent patency was also significantly greater in the ILBT group[43].

Aggarwal *et al*[34] reported an improvement in symptoms such as fatiguability, nausea, vomiting, pain, icterus, pruritis, dyspnea, insomnia, and loss of appetite after palliation with PTBD combined with ILBT[34]. Mayer *et al*[44] reported symptomatic improvement in pruritis and jaundice in all their patients with unresectable bile duct malignancy after biliary decompression with PTBD followed by ILBT. The dose of brachytherapy in their study was 2.5 Gy in 2 fractions *per* day for a total dose of 10 Gy. However, five of their patients also received EBRT[44]. Few of the studies in which brachytherapy has been used with palliative intent, mainly to relieve biliary obstruction, are presented in Table 1.

Complications

The most frequent complication of ILBT is cholangitis[45]. Other side effects of PTBD combined with ILBT include nausea, vomiting, and gastroduodenal ulceration[34].

Limitations

ILBT is not used frequently due to the lack of availability and expertise and patient's moribund condition due to disease. Also, there is paucity of literature, and a lack of survival benefit. But in patients with malignant biliary obstruction, it can be used as an adjunct to systemic therapies. It can be

used as an adjunct to biliary drainage in the palliative setting.

CONCLUSION

ILBT offers an effective means of palliating biliary obstruction in patients with cholangiocarcinoma. The article focuses mainly on the role of ILBT in the palliation of malignant biliary obstruction. ILBT delivers a high dose of radiation to the tumor with sparing of surrounding normal tissues, thus avoiding many of the side effects seen with external beam radiation. The high dose *per* fraction in ILBT can have an ablative effect on the tumor and can lead to better symptom control and quality of life. The transhepatic approach is preferred over the endoscopic technique as ILBT is easier to perform when combined with PTBD as compared to ERCP. ILBT, when combined with these drainage procedures, improves the stent patency rates by inhibiting tumor ingrowth. There is a need for prospective studies to compare the quality of life and outcome in such patients using ILBT.

FOOTNOTES

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MINIREVIEWS

Endoscopic management of difficult laterally spreading tumors in colorectum

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Abstract

Due to the advent of the screening programs for colorectal cancer and the era of quality assurance colonoscopy the number the polyps that can be considered difficult, including large (> 20 mm) laterally spreading tumors (LSTs), has increased in the last decade. All LSTs should be assessed carefully, looking for suspicious areas of submucosal invasion (SMI), such as nodules or depressed areas, describing the morphology according to the Paris classification, the pit pattern, and vascular pattern. The simplest, most appropriate and safest endoscopic treatment with curative intent should be selected. For LST-granular homogeneous type, piecemeal endoscopic mucosal resection should be the first option due to its biological low risk of SMI. LST-nongranular pseudodepressed type has an increased risk of SMI, and en bloc resection should be mandatory. Underwater endoscopic mucosal resection is useful in situations where submucosal injection alters the operative field, *e.g.*, for the resection of scar lesions, with no lifting, adjacent tattoo, incomplete resection attempts, lesions into a colonic diverticulum, in ileocecal valve and lesions with intra-appendicular involvement. Endoscopic full thickness resection is very useful for the treatment of difficult to resect lesions of less than 20 up to 25 mm. Among the indications, we highlight the treatment of polyps with suspected malignancy because the acquired tissue allows an exact histologic risk stratification to assign patients individually to the best treatment and avoid surgery for low-risk lesions. Endoscopic submucosal dissection is the only endoscopic procedure that allows completes en bloc resection regardless of the size of the lesion. It should therefore be indicated in the treatment of lesions with risk of SMI.

Key Words: Colorectal polyps; Laterally spreading tumors; Endoscopic mucosal resection; Underwater endoscopic mucosal resection; Endoscopic full thickness resection; Endo-

scopic submucosal dissection

Core Tip: The number of detected large laterally spreading tumors has increased in the last decade. Herein, we review the current landscape of different endoscopic techniques that allow us to resect difficult laterally spreading tumors. We also describe strategies in problematic situations such as scarred lesions or difficult areas and how to treat adverse events related to colonoscopy.

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INTRODUCTION

Therapeutic endoscopy is nowadays a well consolidated area in the gastroenterology field, covering techniques such as gastroscopy, colonoscopy, enteroscopy, endoscopic retrograde cholangiopancreatography and therapeutic endoscopic ultrasound. In the last decade, techniques for resection of early gastrointestinal neoplasia have become widespread worldwide and gaining popularity among young endoscopists with special interests in learning endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). The main societies have published their statements[1-4].

On the other hand, with the advent of the screening programs for colorectal cancer and adopted in Europe, Australia, Asia and North America and the era of quality assurance and high-definition colonoscopy, the number of advanced mucosal neoplasia and early cancer in the colon, including the polyps that can be considered difficult, has increased in the last decade[5]. The definition of a difficult polyp is not well established. These polyps are typically defined by their size (generally considered as those greater than or equal to 20 mm), morphology, location, biology and previous manipulation (Figure 1).

Thus, the endoscopist should have the skills to detect and characterize all types of colorectal lesions and should be able to predict their risk of deep submucosal invasion (SMI) with high accuracy and proceed to endoscopic resection if it is indicated. The optical diagnosis with image-enhanced endoscopy is the key and mandatory first step before management of a colorectal polyp. First, morphology should be assessed and described according to the Paris Classification, including surface [granular or non-granular in cases of laterally spreading tumors (LSTs) or presence of ulcerations] and looking for demarcated areas (nodules, depressions or marked erythema). Then, virtual chromoendoscopy with blue light technology should be applied to investigate the surface and microvascular patterns. There are different classifications that help predict the risk of deep SMI, like Narrow Band Imaging (NBI) International Colorectal Endoscopic classification that does not need optical zoom or Japan NBI Expert Team (JNET) classification that uses optical zoom. The subclass JNET3 includes deep submucosal invasive lesions; JNET2a includes mostly intraepithelial lesions (*e.g.*, low-grade dysplasia), while that of JNET2b could be found in intramucosal lesions and lesions with SMI. In those cases, pit pattern evaluation with chromoendoscopy and optical zoom using crystal violet or indigo carmine should be recommended, especially in the demarcated areas that may have a higher risk of SMI[6].

The endoscopic treatment of colorectal lesions should be reserved to all early neoplastic lesions with low risk of SMI and thus ideally no risk of lymph node metastasis. If the lesion is considered to have risk of lymph node metastasis, surgery should be considered as a first option.

There is strong evidence now to recommend the EMR as the first-line therapy for non-invasive lesions. It has good results and lesser mortality compared to surgery, and the patients could be discharged the same day (even elderly patients or patients with a severe comorbidity)[7,8].

Herein, we review the techniques for endoscopic resection of the LST, including complex lesions.

LATERALLY SPREADING COLORECTAL TUMORS

The term LST, initially reported by Kudo *et al*[9], refers to flat lesions larger than 10 mm that grow laterally along the colonic wall, being classified as granular (LST-G) and non-granular (LST-NG).

The LST-G can be classified as LST-G homogeneous type (Paris Classification 0-IIa) if they show a granular homogeneous surface (usually < 3 mm) or as LST-G nodular mixed type (Paris Classification 0-

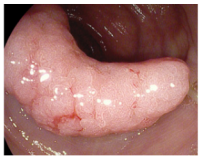
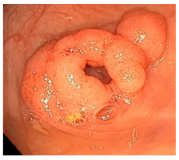
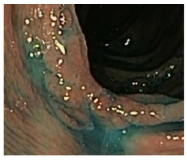
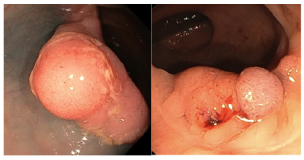
Morphology	Special location	Biology	Previous manipulation
Non-granular morphology; Large sessile; Depressed area	Appendicular orifice; Ileocecal valve; Diverticulum; Anal margin; Flexures	Poor/Non-lifting (Fibrosis, desmoplastic reaction); High impedance (fat); Easy bleeding (arterioles hiding in fat, high density of vessels)	Tattooing; Biopsies/"macrobiopsies;" Prior resection attempt
			

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Figure 1 Characteristics that make a polyp difficult.

II + Is) if they have one or more sessile nodules, with those greater than 10 mm carrying an increasing risk of SMI. The LST-NG can be classified as LST-NG flat type (Paris Classification 0-IIa) or LST-NG pseudodepressed type (Paris Classification 0-IIa + IIc)[10].

Their characteristic growth (lateral rather than vertical) appear to be caused by adequate co-expression of β-catenin and E-cadherin in the basolateral membrane, type IV collagen along the basement membrane and expression of atypical protein kinase λ/ι (an essential cell polarity regulator) like normal colonic mucosa[11].

They also seem to overexpress lipocalin-2 and metallopeptidase-9 in a correlated manner to advanced stages (worse pathology grading), being both suggested as potential serum biomarkers for LST progression[12].

The types of LST have a different biology. For example, the LST-G type express CpG island methylator phenotype-high involving more than two loci and has a high prevalence of *K-ras* mutations (especially in the right colon), whereas the LST-NG type have less *K-ras* mutations and are CpG island methylator phenotype-low[13,14]. New non-invasive diagnostic biomarkers are being explored with the microbiome signature being one of them.

Clinically, the LST-NG type tend to be more aggressive with a higher incidence of advanced carcinoma, especially the pseudodepressed type, with incidences of 19.8%-43.4%. On the other hand, LST-G type tend to have less submucosal carcinoma, being rare in the LST-G homogeneous type (0.5%; 95%CI: 0.1%-1.0%) irrespective of the size of the lesion (Figure 2)[15].

Location is variable. Granular type is more often localized in the cecum and rectum and non-granular in the right colon[16].

For large LST-G homogeneous type, piecemeal EMR should be the first option irrespective of the size of the lesion most of the time due to its biological low risk of SMI. For LST-G nodular mixed type careful inspection of the surface and vascular patterns (specially in nodules > 10 mm) should be done to rule out signs of deep SMI prior to treatment.

For LST-NG type, en bloc resection should be considered as the first option in all cases due to its higher risk of SMI (especially for the pseudodepressed type). Thus, ESD or surgical treatment should be decided according to local expertise in case the lesion is too big for en bloc EMR. Endoscopic full thickness resection (EFTR) may be an alternative if the lesion is suitable.

In some cases, LST-NG flat type might be resected in piecemeal if the surface and vascular patterns show no signs of SMI. These considerations are summarized in Table 1.

ELECTROSURGICAL PRINCIPLES FOR EMR

Knowing the basic principles of diathermy is mandatory for endoscopists. Knowledge on the management of electrosurgery may be able to improve procedural outcomes and safety for our patients [17].

Electrosurgery uses radiofrequency electricity to generate heat in the tissue itself rather than applying heat from an outside source. The snares and most endoscopic knives commonly used in the west are monopolar [the electricity flows from the active electrode (snare) to the neutral electrode placed in the patient skin]. Fortunately, the electrosurgical units use high frequency alternating current (300 kHz to 5 MHz) to avoid neuromuscular stimulation. Thus, the risk of complications is mainly related to the amount of heat produced.

Power is the amount of energy consumed per unit time, and it is measured in watts. The energy dissipated as heat when the electric current (amperes) passes through the resistance (ohms) of the tissue held by the snare is measured in joules. There are two main clinical effects when the electric current is

Table 1 Considerations for endoscopic treatment in laterally spreading tumors

LST suitable for piecemeal EMR	Comments	LST not suitable for piecemeal EMR	Comments
LST-G homogeneous type	Very low risk for deep SMI, independent of size of the lesion	LST-NG pseudodepressed type	En bloc resection
LST-G mixed nodular type with no signs of SMI	Consider en bloc resection first. If not, careful inspection of surface/pit pattern and vascular pattern specially in the larger nodules (≥ 10 mm), resect the nodular area apart (*e.g.*, JNET2a)	LST-G mixed nodular or NG flat with risk of SMI	En bloc resection (*e.g.*, JNET2b, pit pattern V)
LST-NG flat with no demarcated area and no signs of SMI	Consider en bloc resection first. If not, careful inspection of surface/pit pattern and vascular pattern (*e.g.*, JNET2a)		

EMR: Endoscopic mucosal resection; G: Granular type; JNET: Japan Narrow Band Imaging Expert Team; LST: Laterally spreading tumor; NG: Non-granular type; SMI: Submucosal invasion.

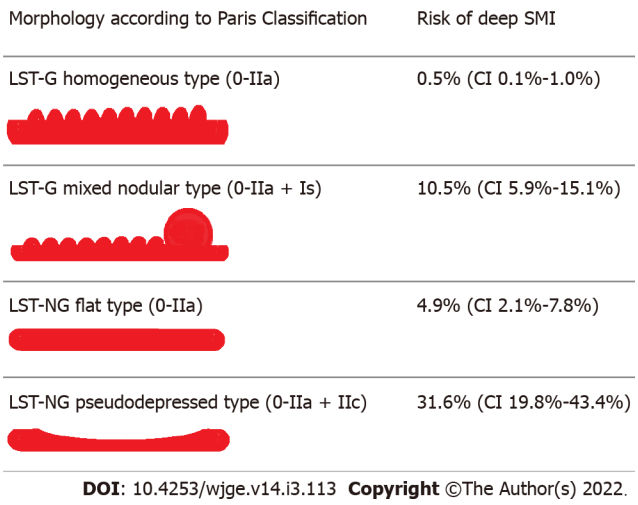

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Figure 2 Risk of submucosal invasion.

applied to the tissue by the snare: boiling (cells burst resulting in cutting tissue) and coagulation. If there is more current per unit of area (current density), then more heat is produced; therefore, the smaller the area of tissue trapped into the snare, a lesser amount of power is needed to heat the tissue.

Electrosurgical cutting is produced when a continuous alternating current with more than 200 voltage peaks is applied to the tissue, raising very rapidly the intracellular fluid temperature and boiling the cells (so they burst) with steam formation. Electrosurgical coagulation is produced if the tissue is heated slowly by an intermittent electric current. The temperature rises within cells, the cells shrink, and the cellular proteins coagulate, turning the tissue white (like the effect of heating the albumin of an egg). However, if current application to the tissue continues, then it produces carbon and smoke. This thermal damage may obscure the specimen margins on pathological evaluation.

If the current used has less than 200 voltage peaks, then the effect would be a superficial "pure coagulation" (*e.g.*, SOFT COAG mode in ICC 200 and VIO 300D; ERBE, Tüebingen, Germany). If the current used has more than 200 voltage peaks and is activated 10% or less of the time (of the duty cycle, the fraction of time current flows each second that the activating pedal is depressed), then it would produce a deep coagulation (FORCED COAG mode of ERBE has 4% duty cycle). Even the "purest" cutting current can have some coagulation effect in the tissue around the cutting area where there is not enough heating to boil the cells but to dehydrate and coagulate proteins. Thus, the more cutting or coagulating effect would depend on the duty cycle. The more time energy is delivered by pushing the pedal, the greater the heat is produced and the chances of having a thermal-related complication, such as deep muscle layer injury or perforation.

To perform an EMR, alternating cutting and coagulating output is very useful (*e.g.*, in the ENDOCUT mode of ERBE that alternates cutting current with SOFT COAG). For ERBE VIO 300, it would be recommended to use ENDO CUT Q effect 3 (cut duration 1, cut interval 6) for cutting and SOFT COAG Effect 4 (max. watts 80) for snare tip soft coagulation. The power settings (if they are not self-regulated by the electrosurgical units) should be adapted to the instrument used according to the manufacturer's recommendation, and it is recommended to use the lowest power that will allow the resection[18].

Once we have set the mode and power, we can control by closing the snare on the area of tissue to resect (smaller area, less current needed for tissue cell burst) and the time we deliver that power to the tissue by pressing the pedal. The timing of the pedal is also very important during ESD.

MATERIALS

Endoscope

Nowadays, endoscopes with optical narrow band technology using "blue light" to display the mucosa and vessels in high contrast, such as NBI (Olympus, Tokyo, Japan), Blue Light Imaging (Fujifilm, Tokyo, Japan) or i-scan Optical Enhancement (Pentax, Tokyo, Japan), should be used for endoscopic assessment of the lesion prior to resection, especially if there is optical magnification, to rule out signs of SMI[19].

Olympus has recently incorporated new postprocessing functions in the EVIS X1 system that includes extended depth of field and texture and color enhancement imaging that improves the visibility using white light endoscopy and red dichromatic imaging that enhances the visibility of deep blood vessels and bleeding. These functions could help diagnose and manage complications.

To facilitate resection for polyps in the rectosigmoid area and proximal colon, a gastroscope and a pediatric colonoscope or a short colonoscope may be used, respectively[20]. New colonoscopes like the RetroView™ EC34-i10T, PCF-H190TL/I EVIS EXERA III (Olympus) and Eluxeo EC-740TM/TL [Treier Endoscopie (part of the Duomed Group), Beromünster, Switzerland] provide excellent maneuverability due to a smaller bending radius of the distal tip, and 210° deflection is ideal for the detection and treatment of hard-to-reach lesions.

CO_2

CO_2 insufflation is highly recommended for therapeutic colonoscopy. It reduces pain after EMR of LSTs, which might be a cause of admission, especially in patients with a long duration of polypectomy[21].

Injection solution

A solution mixed with a blue dye is commonly used. The submucosal solution could be a crystalloid like normal saline solution or a colloid solution like glycerol or a succinylated gelatin. The inexpensive succinylated gelatin (gelafusine, gelafundin) was shown to be superior to saline solution requiring fewer injections, resections and an overall reduced EMR time[22]. A meta-analysis showed that use of viscous solutions during EMR leads to higher rates of en bloc resection and lower rates of residual lesions compared with normal saline solution especially with colonic polyp greater than 2 cm[23]. Nonetheless, research to determine the ideal submucosal injection is still ongoing.

Eleview® (Cosmo Pharmaceuticals, Dublin, Ireland), ORISE™ gel (Boston Scientific, Marlborough, MA, United States) and LiftUp® (Endotherapuetics, Australia) are synthetic solutions that were specifically designed to provide a submucosal cushion of optimal height and duration[24,25]. When compared to normal saline solution, Eleview® has demonstrated better cushion-forming ability and a duration of lift of up to 45 min. A double-blind randomized controlled trial comparing Eleview® with saline showed that the mean injected volume was significantly lower, and there was a trend towards shorter procedure and a lower number of resection pieces with this new solution. Despite all these advantages, larger, multicenter, prospective controlled trials are required to compare performance of Eleview®, ORISE™ gel and LiftUp® to other available viscous submucosal solutions for EMR and ESD.

An inert dye such as indigo carmine (or alternatively methylene blue) is added to stain the submucosal layer blue and facilitate the delineation of the lesion margins. The authors do not use adrenaline for submucosal injection, but diluted adrenaline (1/100000-1/300000) could be added according to the preferences of the endoscopist[26].

Transparent cap

The distal cap attachment may contribute to stabilize the tip of the scope, improve visualization of the operative field and facilitate resecting lesions in difficult locations[27]. They are especially useful to create tension of submucosal fibers during ESD. Conic shaped short ST hood may be useful for non-lifting and other complex lesions when access to submucosal space could be difficult.

Premedication

Deep sedation is preferred by the authors for EMR or underwater EMR (UEMR). Prophylactic antibiotics should be considered in cases of EMR or ESD of LST in the distal rectum (as drainage bypasses the liver) especially when a large resection defect ($\geq$ 4 cm) is expected[28]. Consider buscopan or glucagon to reduce bowel peristalsis during the procedure.

Snares

The choice of a specific snare may rely on size and morphology of the lesion, its location, the endoscopist technique and preference or what type of snare is familiar. There are some snares that

combine different sizes and shapes, but no clear benefit of one shape over the other has been demonstrated[2]. In cases of cold EMR, a dedicated cold snare is recommended. For hot EMR and UEMR, the authors' preference is a rounded stiff snare 15 mm for most cases.

ESD knives

Like the choice of snare, it may depend on the lesion and the endoscopist preference. There are many types of ESD knives, but it is highly recommended to have water-jet or water injection capability to save time during dissection.

APPROACH

Endoscopic preoperative optical diagnosis

The most important step is to provide a good endoscopic diagnosis of the lesion, to be sure that the endoscopic resection would have a curative intention. The only way the endoscopic resection will be curative is if all the neoplastic cells are within the lesion we resect, even if they are malignant cells. But if there is a distant spread of the neoplastic tissue (*e.g.*, lymphatics), then the treatment will not be curative. By endoscopic inspection we can predict the risk of deep SMI, telling us that there could be a risk of lymph node metastases. That is why during preoperative evaluation the endoscopist should rule out signs of deep SMI.

The endoscopist should use the best scope (better if there is magnification or dual focus with optical narrow band "blue light" technology), use Paris classification to describe the morphology of the lesion and assess demarcated areas of risk of SMI, such as the nodular and depressed areas. This assessment should focus on pit pattern and vascular pattern.

The JNET Classification was proposed in 2016 according to NBI magnifying endoscopy[6]. It consists of the following four categories, combining vessel and surface patterns: Type 1, the hyperplastic polyp or sessile serrated adenoma/polyp with "invisible" vessel pattern with regular dark or white spots similar to surrounding normal mucosa; Type 2A, the adenoma with low grade dysplasia, with regular vessels (in caliber and distribution) and surface pattern (corresponding to pit pattern III or IV); Type 2B, the adenoma with high grade dysplasia, or sometimes shallow submucosal cancer, with moderately distorted vessels and irregular or obscure surface pattern (corresponding to pit pattern Vi); and Type 3, an invasive cancer with amorphous areas with markedly distorted vessels or avascular areas.

However, in a retrospective study from prospectively collected records (n = 1402 lesions), Type 2B presented low sensitivity (42%) even among expert Japanese endoscopists. Therefore, some authors have suggested that Type 2B requires further investigation using pit pattern diagnosis to differentiate the Vi (irregular; superficial SMI) and Vn (non-structural; deep SMI)[29].

If there is a high suspicion of deep SMI, the patient should undergo a surgical procedure or an endoscopic technique for en bloc resection. It is also very important to delimitate the margins of the lesion, especially if it is a serrated adenoma.

In the LST-G homogeneous type (Paris 0-IIa) of any size, the risk of deep SMI is very low, which makes EMR almost always suitable[2-4,15].

EMR

"Classic" EMR is based on inject and resect technique (Table 2). It may be helpful for en bloc resection of lesions up to 2 cm and for piecemeal resection in bigger LSTs. For piecemeal resection 10 mm to 15 mm snares are usually recommended. For cold EMR, a specific cold snare is recommended. For a successful piecemeal EMR the resection should be performed in a systematic manner, sequentially from the first point of resection or entry in the submucosal plane, including 2-3 mm of apparently normal mucosa at the borders and including the edge of the advancing mucosal defect to avoid islands and bridges of neoplastic tissue.

The final mucosal defect should be checked for signs of injury or residual tissue. It is useful to use a topical submucosal chromoendoscopy with indigo carmine to rule out deep injury. It can be injected or sprayed superficially over the defect with the needle catheter close. The submucosa would pick up the blue color. If there is muscle layer exposed, then it would remain unstained[4,30].

After finishing piecemeal EMR, snare tip coagulation of the normal appearing margins and mucosal defect using SOFT COAG 80W is beneficial as it can reduce 4-fold the rate of residual or recurrent adenoma[4,30,31] even after en bloc EMR.

UEMR

UEMR, described by Nett *et al*[32] in 2012, has been shown to enable safe resection of LST. UEMR is performed by aspirating all the gas from the colonic lumen and instilling water or saline to fill the cavity. The colonic lesion "floats" in a lumen filled with fluid, and the muscularis propria retains a circular configuration and does not follow involutions of the mucosa and submucosa even during peristaltic contractions (Figure 3), making it easier to snare the lesion[33] (Table 2).

Table 2 Steps for endoscopic mucosal resection of laterally spreading tumors

Steps for endoscopic resection	
(1) Endoscopic evaluation	Using Paris classification, pit pattern and vascular pattern to characterize the lesions and define the risk of deep SMI
(2) Strategy	Decide en bloc *vs* piecemeal resection according to risk of SMI. Consider patient position and gravity
(3) EMR technique	
Injection	Needle tangential to the plane. Inject whilst "stabbing" the mucosa helps accurately find the SM plane. Use a dynamic injection technique
Resection	Put the area to resect ideally between 5-6 o'clock (with colonoscope); accommodate the snare over the lesion and push "down," aspirate to decrease tension and maximize tissue capture; close the snare tightly; check for mobility and degree of closure of the snare handle (usually < 1 cm distance between thumb and fingers), be sure there is no muscle trapped, otherwise release the tissue (in case of doubt, open and close the snare to "drop out" possible muscular entrapment); press the pedal to resect
Wash and check mucosal defect	Check the mucosal defect produced to rule out signs of muscle layer damage or perforation
Hemostasis	If there is mild intraprocedural bleeding, try first snare tip soft coagulation. If necessary, coagulating forceps or clips can be helpful
Systematic inject and resect	Continue resection injecting when necessary to maintain submucosal cushion. Resect 2-3 mm of normal mucosa to ensure margins. Try not to leave islands or bridges between resections
(4) UEMR technique	
Water filling	Aspirate all the gas and fill the lumen of the working space with water or saline (turning off insufflation may help) to create a gravity-free environment
Resection	Put the area to resect ideally between 5-6 o'clock (with colonoscope); accommodate the snare over the lesion "torque and crimp" and push "down" to get the floating lesion inside the snare; aspirate and irrigate more water to help the capture of the tissue; close the snare tightly and separate the tissue from the wall. Press the pedal to resect. Underwater, higher outputs might be needed for resection/coagulation due to the heat sink effect
Wash and check mucosal defect	Check the mucosal defect produced to rule out signs of muscle layer damage or perforation. As no dye is used to stain the submucosa, the operator should become familiarized with the aspect of the "transparent" fibers
Hemostasis	In cases of jet bleeding gas insufflation might be needed to find the bleeding point
Systematic gas aspiration water irrigation and resection	Continue resection aspirating gas or irrigating water when necessary. Resect 2-3 mm of normal mucosa to ensure margins. Try not to leave islands or bridges between resections
(5) Final inspection	Check the scar to rule out residual neoplastic tissue or signs of deep injury. In cases of piecemeal resection, thermal ablation with the tip of the snare (Soft COAG 80 W) to coagulate the mucosal borders of the scar reduces risk of recurrence
(6) Specimen retrieval and assessment	Consider using a net for retrieval. Big nodules should be sent separately if it was piecemeal resection

EMR: Endoscopic mucosal resection; SM; Submucosal; SMI: Submucosal invasion; UEMR: Underwater endoscopic mucosal resection

In recent years, meta-analysis has supported that UEMR resection achieves a higher en bloc resection rate and less post-endoscopic resection recurrence compared to conventional EMR, especially when polyps greater than or equal to 20 mm are resected. In contrast, no significant differences were detected with respect to the occurrence of adverse events[34,35].

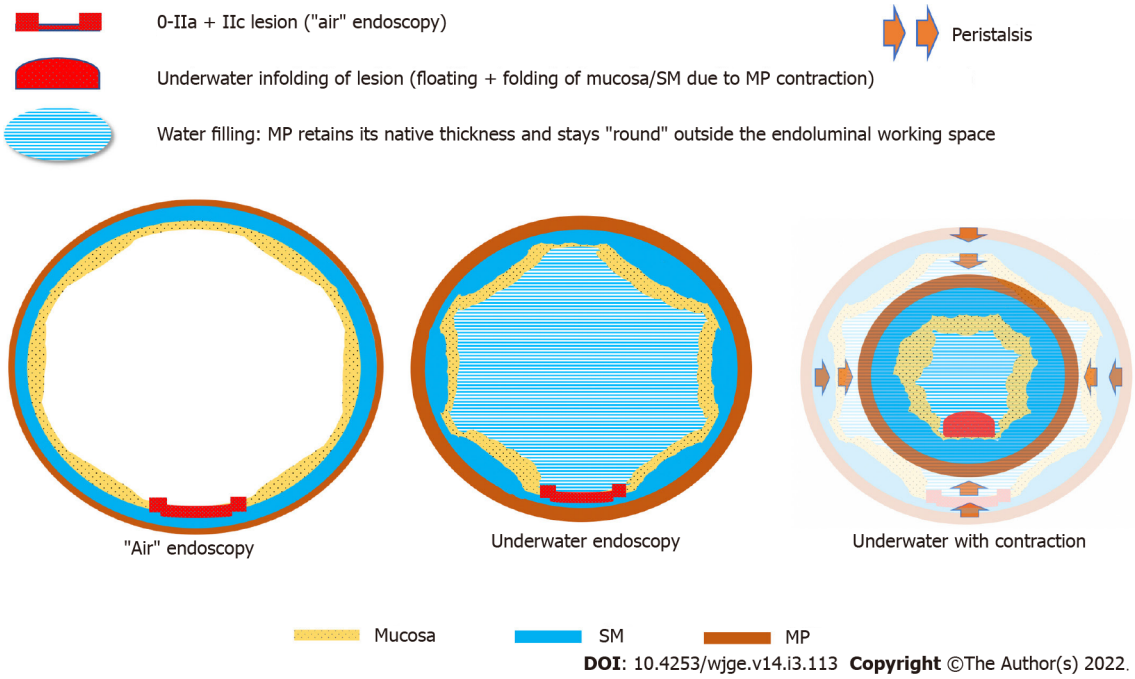
In daily clinical practice, UEMR is very useful due to its effectiveness, safety and easy learning. This technique can be used for the resection of scar lesions with no lifting, adjacent tattoo, incomplete resection attempts, lesions into a colonic diverticulum, in the ileocecal valve with ileal component and lesions with intra-appendicular involvement[36].

UEMR may also be useful for en bloc resection of pseudodepressed less than or equal to 2 cm LST-NG in which en bloc resection is mandatory due to the high risk of SMI[33].

Another advantage of UEMR is that it is a "reversible" technique. In the case that en bloc resection of a high-risk lesion does not seem feasible, all the water can be aspirated, and the technique can be changed either to ESD or EFTR.

EFTR

EFTR is an emerging technique for removal of complex colorectal lesions. Since the introduction of the full thickness resection device (FTRD; Ovesco Endoscopy AG, Tübingen, Germany) in Germany in 2014 [37] several studies have reported encouraging results on the short-term safety and efficacy of EFTR[38, 39].



DOI: 10.4253/wjge.v14.i3.113

Figure 3 During muscularis propria contraction, infolding of the 0-IIa + IIc lesion occurs. Citation: Uchima H, Colán-Hernández J, Binmoeller KF. Peristaltic contractions help snaring during underwater endoscopic mucosal resection of colonic non-granular pseudodepressed laterally spreading tumor. *Dig Endosc* 2021; 33: e74–6. Copyright ©The Author(s) 2021. Published by John Wiley & Sons Australia, Ltd[33].

To perform an EFTR, the lateral margins of the lesion are first marked with the probe that is part of the set or by other means (*e.g.*, snare tip coagulation or argon plasma). Thereafter, the colonoscope is retracted, and the FTRD is mounted and advanced to the target lesion. The lesion is then pulled into the resection cap with the grasping forceps. After deployment of the clip, the snare is closed, and the tissue is cut. To avoid unintended incorporation of organs next to the colonic wall, traction of the target lesion without suction is recommended, and when necessary, suction should be performed very gently and with caution. After resection, the specimen is recovered, and inspection of the resection site to check for the correct position of the over-the-scope clip is mandatory. For colonic lesions, prOVECAP (Ovesco Endoscopy, Tübingen, Germany), a cap similar in size to the FTRD cap, can be mounted on the instrument tip to evaluate accessibility to the target lesion. The keys to technical success are the right size of the lesion, performing correct traction and coordinated teamwork[40].

General indications for EFTR are residual adenoma after endoscopic resection, non-lifting sign adenoma, histological R1 resection (deep and lateral positive margins at histology), suspected T1 carcinoma, adenomas at difficult anatomic locations (appendiceal orifice, diverticulum, folds) and subepithelial lesions[38,39].

Among the indications for EFTR, we highlight the treatment of polyps with suspected malignancy due to its clinical impact because in most cases the acquired tissue allows an exact histologic risk stratification to assign patients individually to the best treatment and avoid surgery for low-risk lesions. In a retrospective multicenter study that included 64 patients with incomplete resection of malignant polyps, the performance of EFTR obviated the need for surgery in most of these patients (84%) by classifying them as low risk and therefore may be the method of choice for this indication[41].

A recent meta-analysis including nine studies conducted in European countries with 469 Lesions showed a pooled rate of technical success, full thickness resection and R0 resection of 94.0% (95%CI: 89.8%-97.3%), 89.5% (95%CI: 83.9%-94.2%) and 84.9% (95%CI: 75.1%-92.8%), respectively; a pooled estimate of bleeding, perforation and post-polypectomy syndrome of 2.2% (95%CI: 0.4%-4.9%), 0.19% (95%CI: 0.00-1.25%) and 2.3% (95%CI: 0.1%-6.3%), respectively and pooled rates of residual/recurrent adenoma and surgery for any reason of 8.5% (95%CI: 4.1%-14.0%) and 6.3% (2.4%-11.7%), respectively. These results show that EFTR with an FTRD system is efficient and safe for treating non-lifting and invasive colorectal lesions with conventional EMR and ESD criteria[42]. Nonetheless, future studies are needed to investigate the role of EFTR in large colorectal lesions and specify its indications.

ESD

ESD was first described in Japan for the treatment of early gastric cancer and adopted for the treatment of colonic lesions. It is the only procedure that allows complete en bloc resection regardless of the size of the lesion.

It is a technically demanding procedure, requires a long learning curve and requires a longer procedure time than EMR[43]. Adverse events are more common for ESD than for EMR, with published perforation rates of about 5%[44]. Nevertheless, the safety profile is adequate because almost all ESD complications can be managed endoscopically, and the risk of surgery related to post-ESD complications (2%) is low[45].

It basically consists of entering the submucosal space, which is a virtual space that we will create with a solution injected into the submucosa. The classic technique includes marking the lesion to be resected and injecting a lifting agent into the submucosa at its periphery. Using the endoscopic knife, the mucosa is incised circumferentially, and the lesion is separated from the muscularis propria. Additional submucosal injections are performed as necessary to lift the central portion of the lesion to allow for complete resection. Other strategies for ESD have been described, such as pocket-creation method or tunnel[46]. Traction is recommended for colonic lesions, *e.g.*, using rubber band-clip technique because it can significantly decrease the procedure time, increase the en bloc resection rate and the R0 resection rate[47].

There are several tips thoroughly commented on elsewhere in the literature[48].

Post-procedural care

If there is no complication during the procedure and there are no special risk factors, then the patient could be discharge within 1-3 h after EMR/UEMR or ESD of small lesions, or 24 h or less after EFTR. If there are symptoms, risk factors for complications or special situations (very large lesion), then a longer period of observation might be consider. If there is any sign of complication (pain with abdominal distension, vomiting, rectal bleeding, fever) perform a blood test and or computed tomography scan according to the clinical suspicion and act according to the results. If perforation with peritonitis is suspected, then surgery should be evaluated[49].

COMPLICATIONS

Deep mural injury and perforation

It is very important to differentiate post-polypectomy syndrome, a benign complication with a good prognosis in most cases that can be treated medically[50], secondary to excess coagulation and thermal injury of the colonic wall in which computed tomography scan may show a severe mural thickening with stratified enhancement pattern with surrounding infiltration but no air[51]. It is extremely important to recognize deep mural injury (DMI) signs such as the target sign during or immediately after finishing the EMR using the Sydney Classification of DMI (Table 3)[52].

The right colon (and cecum) is the thinner part of colon and might be more prone to complications such as perforation, but in one study it seemed that the transverse colon might have more incidence of DMI. The transverse colon is highly mobile, and it has a long mesentery. It is possible that the muscular propria could be more mobile and be trapped easily without "feeling" that we snare the muscular layer.

If there are signs of DMI, then an endoscopic treatment could be offered according to the experience of the endoscopist by using through-the-scope clips for iatrogenic perforations less than 1 cm and the use of the over-the-scope clip could be considered for defects 1-2 cm[53]. For larger iatrogenic perforations, endoscopic treatments with endoscopic suturing or a polyloop and clips method using a double-channel or single-channel endoscope have been described[54,55].

Prophylactic clipping of muscular injury (target signs) might protect against delayed clinical perforation. If the perforation had leakage of colonic fluid, then a surgical approach might be a better option.

Bleeding

Bleeding is a frequent complication of EMR and ESD. Intraprocedural bleeding (IPB) is relatively common, being most of the time an auto limited event from cutting small capillary vessels or vessels that may require coagulation. The IPB rate in the literature is over 10%. In an observational multicenter study that analyzed data from EMR of sessile colorectal polyps greater than or equal to 20 mm in size (mean size: 35.5 mm) of 1172 patients, IPB was observed in 133 (11.3%)[56].

The small bleeding during procedure could be minimized by adding diluted adrenaline to the submucosal injection solution and could be treated with coagulating current using the tip of the snare (*e.g.*, ERBE soft coagulation 80 W, snare tip soft coagulation), coagulating forceps or hemostatic clips[17].

IPB that requires endoscopic treatment is associated with a longer procedure time, higher risk of clinically significant post procedural bleeding and recurrence at first surveillance after piecemeal EMR [56].

Post procedural bleeding is also relatively frequent. In a prospective study involving 1039 patients after EMR, 6% had a clinically significant delayed post-polypectomy bleeding, 21% of them (13 patients) being unstable and 26% (16 patients) requiring blood transfusion. Most of the patients (55%) were managed conservatively, 44% underwent colonoscopy, and 1 patient required primary embolization and surgery[57].

Table 3 Sydney Classification of deep mural injury

Sydney Classification of deep mural injury	
Type 0	Normal defect. Blue mat appearance of obliquely oriented intersecting submucosal connective tissue fibers (with a blue dye such as indigo carmine or methylene blue)
Type 1	MP visible but no mechanical injury ("Whale" sign)
Type 2	Focal loss of the submucosal plane raising concern for MP injury or rendering the MP defect uninterpretable
Type 3	MP injured, specimen target sign or defect mirror target sign identified
Type 4	Actual hole within a white cautery ring, no observed contamination
Type 5	Actual hole within a white cautery ring, observed contamination

MP: Muscular propria.

To control the active bleeding after EMR or ESD, mechanical therapy (*e.g.*, through-the-scope/cap-mounted clips) and/or contact thermal coagulation are helpful. In cases of inadequate or failed hemostasis with ongoing bleeding, hemostatic topical agents can be used as a secondary treatment option[58].

The risk factors for clinically significant delayed post procedural bleeding include lesions larger than 3 or 4 cm, located in the proximal colon, elderly patients, patients with major comorbidities, taking antiplatelets and absence of use of epinephrine. Two scores have been published to predict the risk of delayed bleeding in two different populations, with similar results summarized in Table 4[59,60].

Prophylactic endoscopic coagulation with a coagulating forceps (with low-power coagulation) does not seem to significantly decrease the incidence of clinically significant post-EMR bleeding. Nonetheless, a recent meta-analysis has shown benefit when clipping polyps measuring greater than or equal to 20 mm, especially in the proximal colon[61].

In recent years, coverage agents have been developed to cover large mucosal defects that appear to be effective in the prevention of late complications, but randomized controlled trials and head-to-head comparative studies of shielding products are still needed[62].

RECURRENCE OR RESIDUAL NEOPLASTIC TISSUE AND SURVEILLANCE

Recurrence or residual neoplastic tissue after EMR can be easily solved endoscopically in most of cases during surveillance since treatment after first revision is usually successful.

Early recurrence of large conventional adenomas seems to be around 16% at first surveillance colonoscopy (SC), with a cumulative recurrence around 20% after second SC 1 year after and around 28% after 2 years. Large sessile serrated adenomas/polyp recurrence seems to be lower, at about 7% from 12 mo onwards[7].

First SC at 3-6 mo after piecemeal EMR of polyps greater than or equal to 20 mm is recommended for scar assessment and the intervals to the next colonoscopy at 1 year and then 3 years[4,30]. It has been published that after EMR of lesions smaller than 4 cm without significant intraprocedural bleeding (not requiring endoscopic treatment) and with low-grade dysplasia, the first SC can be safely scheduled at 18 mo. The Sydney EMR recurrence tool (Table 5) was developed to help predict the risk of recurrence after piecemeal EMR, with a 92% negative predictive value for recurrence at first SC, for Sydney EMR recurrence tool 0 lesions[63]. It is also very important to treat other synchronic lesions, clear the rest of the colon or rule out a serrated polyposis in cases of resection of large serrated lesions.

It is very important to carefully inspect the scar. The scar might be identified as a pale area with disruption of vascular pattern or fold convergence. All the edges and center of the scar should be interrogated, looking for a transition point where a non-neoplastic pit or vascular pattern turns into a neoplastic pattern (Kudo pit pattern, NBI International Colorectal Endoscopic and JNET classification) and being aware of post-EMR scar clip artifact using a high-definition endoscope with optical narrow band technology[64].

In surveillance cases with local recurrence, endoscopic resection with repeat EMR, snare or avulsion method can be performed, and ablation of the perimeter of the post-treatment site may be considered. If there is a retained clip in the scar, the procedure should be the same. In case there is a suspicious area of residual polyp, the retained clip should not prevent endoscopic resection of the residual tissue[4,30].

Table 4 Spanish Score for risk of bleeding after endoscopic mucosal resection

	Age ≥ 75-yr-old	Lesion ≥ 40 mm	ASA III-IV	Location proximal to transverse colon	Aspirin	Clips
Yes	1	1	1	3	2	0
No	0	0	0	0	0	2
Risk of bleeding after EMR						
Low risk 0.6% (0.2%-1.8%)	0-3 points					
Medium risk 5.5% (3.8%-7.9%)	4-7 points					
Elevated risk 40% (21.8%-61.1%)	8-10 points					

ASA: American Society of Anesthesiologists classification of physical health; EMR: Endoscopic mucosal resection.

Table 5 Sydney endoscopic mucosal resection recurrence tool

Risk factor	Score
LST size ≥ 40 mm	2
IPB requiring endoscopic control	1
High-grade dysplasia	1
Total	4
Cumulative incidence of EDR% (standard error)	
SERT = 0	9.8% (2.2); 6 mo FU
	11.6% (2.5); 18 mo FU
SERT = 1-4	23.0% (2.5); 6 mo FU
	36.3% (3.2); 18 mo FU

EDR: Endoscopically determined recurrence; FU: Follow-up; IBP: Intraprocedural bleeding; LST: Laterally spreading tumor; SERT: Sydney endoscopic mucosal resection recurrence tool.

SPECIAL AND PROBLEMATIC SITUATIONS

The actual problems of EMR are the treatment of fibrotic tissues or non-lifting tissues as well as difficult areas for endoscopic resection.

Peri/intra-appendicular orifice lesions

In this scenario, EMR is a technical challenge because of difficult endoscopic access due to the narrow lumen of the appendix and thin colonic wall at the base of the cecum, which means a high risk of perforation. Nonetheless in expert hands, it is a safe and effective treatment, but if more than 50% of the circumference of the appendicular orifice (AO) is involved, then surgery should be considered[65]. As it is a narrow area, injection must be small to avoid narrowing the working field, and use of mini snares is helpful.

UEMR has been shown to enable safe resection of AO lesions, especially those limited to the rim. In a series of 27 consecutive patients with AO adenomas (median size 15 mm, range 8-50 mm), 89% successful resection was achieved, with 59% of lesions being resected en bloc. Post-polypectomy syndrome occurred in 7% of cases. No other complications occurred, and over a median follow-up of 29 wk only 10% of patients (n = 2) had residual adenoma present[66].

With underwater submersion, the appendix can partially evert into the cecal lumen, and the colonic lesion "floats" in a lumen filled with water. This allows endoscopic resection without previous submucosal injection, which makes lesions that affect the AO more accessible to endoscopic resection. To maximize tissue capture, contraction of the muscularis propria followed by the torque-and-crimp technique can be expected with the open loop[32]. In cases of residual tissue deep in the AO, a combination of air suction and more water infusion can help to evert residual tissue, making it accessible for snare resection[36].

ESD for lesions located in close proximity to the AO remains a challenging technique. In a retrospective study that included 76 lesions, en bloc resection was achieved in 72 (94.7%) and median tumor size was 36 mm (10-110 mm). One patient experienced intraoperative perforation, was treated by

clip closure, later developed appendicitis and underwent emergency ileocecal surgical resection; another patient experienced postoperative appendicitis and recovered with antibiotic treatment. Despite the challenges of working in the region of the cecum and AO, this study demonstrates that ESD performed by skilled and experienced endoscopists can be a safe and effective technique[67].

EFTR is another endoscopic treatment option. In a multicenter study in Germany that included 50 lesions, with mean size of 18 mm, EFTR was technically successful in 48 (96%), and R0 resection was achieved in 32 patients (64%). Post interventional appendicitis occurred in 7 patients (14%) during follow-up, and conservative treatment was sufficient in half of the cases[68]. The authors believe that the EFTR of appendicular lesions is a promising modality in a certain group of patients, but further studies are required to prospectively evaluate the feasibility and safety of this technique.

Islands or bridges of neoplastic tissue during EMR

A new injection and a mini/small snare should be tried. If it is not possible to snare, then sometimes the suction pseudopolyp technique or precutting with the tip of the snare around the non-lifting area may help. Otherwise, cold avulsion with forceps and snare tip soft coagulation/ablation of the scar area seems to be helpful in small areas of benign residual tissue. In this situation, UEMR and band ligation with or without resection can also be performed.

Scarred lesions

If it is not possible to resect with the inject and resect technique, then the non-lifting part of the lesion could be resected by cold avulsion (forceps), pre-cutting EMR[69], UEMR, ESD, EFTR[42] or surgery (the latter especially if there are suspicious areas of SMI). The same recommendation would apply to fibrotic lesions secondary to tattoo, multiple biopsies, the biology of the lesion or SMI, showing non-lifting sign, "jet sign" or canyoning. The authors find UEMR especially useful in this situation for benign lesions. As it is a "reversible" technique, if it is not suitable, then another technique like ESD or EFTR could be performed during the same session. If there is suspicion of malignancy, then surgery or EFTR might be preferable.

LST at the ileocecal valve

It is very important to define the borders of the lesion and if the ileum is involved, then sometimes a cap is helpful[27]. In cases of classic EMR, the amount of submucosal injection should be small if there is a flat lesion over the ileocecal valve to avoid excessive tension in the submucosal cushion since it is very easy that the snare slips while closing in this situation. A mini snare may be helpful when the ileum is involved. It is a safe procedure, and stenosis after EMR seems to be rare. Although it is complex, successful EMR seems to be greater than 90% in experienced hands. Extensive involvement of the terminal ileum or both ileocecal valve lips are associated with EMR failure[70]. UEMR is a good option, and the one preferred by the authors at this location.

Anorectal lesions

Because of the innervation in distal rectum, the use of long-acting local anesthetic (ropivacaine or bupivacaine) in the submucosal injectate (avoiding intravascular injection and requiring cardiac monitoring) for submucosal injection around the anorectal region and prophylactic antibiotics should be considered[28]. The use of a gastroscope for increased mobility and retroflexion may be helpful. It is safe to perform the endoscopic resection over the dentate line and hemorrhoidal columns. When performing ESD at this location, the operator should be aware that there could be muscular fibers on the submucosal layer on this location (it is the exception in the gastrointestinal tract).

Tough colonoscopy

It is a subjective term, which covers different situations, such as scope instability. Working using retroversion (easier with a gastroscope or a pediatric colonoscope) might stabilize the endoscope facilitating the resection sometimes. In the proximal colon, a distal attachment such as Endocuff or using a balloon enteroscope or a double balloon platform (Dilumen, Lumendi, Westport, Conn, United States) might help to stabilize the scope.

CONCLUSION

There are different endoscopic techniques for the resection of complex colorectal LST that the therapeutic colonoscopist should be aware of. EMR (inject and resect) is useful for most colorectal benign lesions. UEMR is a very useful technique since it avoids the need for submucosal injection. It might be a very good alternative in non-lifting lesions or in difficult locations like ileocecal valve, AO, narrow sigmoid or peridiverticular area where there is a narrow space where injection could make the access more difficult. ESD is the only technique that allows en bloc resection regardless of the size of the lesion, being especially useful for large LSTs that harbor risk for SMI, for example large LST with big

nodules in the rectosigmoid area. EFTR on the other hand is the technique that allows the deepest margins and because of that might be the best choice for endoscopic resection of less than 2.5 cm suspected malignant LST.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Endoscopic ultrasound-guided through-the-needle microforceps biopsy and needle-based confocal laser-endomicroscopy increase detection of potentially malignant pancreatic cystic lesions: A single-center study

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Abstract

BACKGROUND

Currently, there is insufficient data about the accuracy in the diagnosing of pancreatic cystic lesions (PCLs), especially with novel endoscopic techniques such as with direct intracystic micro-forceps biopsy (mFB) and needle-based confocal laser-endomicroscopy (nCLE).

AIM

To compare the accuracy of endoscopic ultrasound (EUS) and associated techniques for the detection of potentially malignant PCLs: EUS-guided fine needle aspiration (EUS-FNA), contrast-enhanced EUS (CE-EUS), EUS-guided fiberoptic probe cystoscopy (cystoscopy), mFB, and nCLE.

METHODS

This was a single-center, retrospective study. We identified patients who had undergone EUS, with or without additional diagnostic techniques, and had been diagnosed with PCLs. We determined agreement among malignancy after 24-mo follow-up findings with detection of potentially malignant PCLs *via* the EUS-guided techniques and/or EUS-guided biopsy when available (EUS malignancy detection).

RESULTS

A total of 129 patients were included, with EUS performed alone in 47/129. In 82/129 patients, EUS procedures were performed with additional EUS-FNA (21/82), CE-EUS (20/82), cystoscopy (27/82), mFB (36/82), nCLE (44/82). Agreement between EUS malignancy detection and the 24-mo follow-up findings was higher when associated with additional diagnostic techniques than EUS alone [62/82 (75.6%) *vs* 8/47 (17%); OR 4.35, 95%CI: 2.70-7.37; $P < 0.001$]. The highest malignancy detection accuracy was reached when nCLE and direct intracystic mFB were both performed, with a sensitivity, specificity, positive predictive value, negative predictive value and observed agreement of 100%, 89.4%, 77.8%, 100% and 92.3%, respectively ($P < 0.001$ compared with EUS-alone).

CONCLUSION

The combined use of EUS-guided mFB and nCLE improves detection of potentially malignant PCLs compared with EUS-alone, EUS-FNA, CE-EUS or cystoscopy.

Key Words: Pancreatic cysts; Endoscopic ultrasound-guided fine-needle aspiration; Confocal microscopy; Image-guided biopsy

Core Tip: This retrospective study compared the accuracy of endoscopic ultrasound (EUS) and associated techniques such as EUS-guided fine needle aspiration (EUS-FNA), contrast-enhanced EUS (CE-EUS), EUS-guided fiberoptic probe cystoscopy (cystoscopy), EUS-guided direct intracystic micro-forceps biopsy (mFB), and EUS-guided needle-based confocal laser-endomicroscopy (nCLE) for the detection of potentially malignant pancreatic cystic lesions (PCLs) in 129 patients. Patients were allocated to three cohorts: those evaluated *via* EUS alone; *via* EUS-FNA, CE-EUS and/or cystoscopy; and with mFB plus nCLE. We observed that combining EUS, mFB, and nCLE had a statistically significant improved detection of potentially malignant PCLs compared to any of the evaluated techniques alone.

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INTRODUCTION

The incidence of pancreatic cystic lesions (PCLs) is rising mainly in elderly patients[1]. Therefore, early detection of potentially malignant PCLs increases the possibility of a curative approach. Current American Gastroenterological Association guideline recommends magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatography (MRCP) to assess PCLs[2]. For the same purpose, the revised Fukuoka guideline recommend computerized tomography (CT), MRI or MRCP, keeping endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) for intraductal papillary mucinous neoplasm (IPMN) evaluation[3]. Nevertheless, both guidelines showed an unsatisfactory pooled sensitivity for malignant PCLs of 64% and 59%, respectively[4].

EUS is the most sensitive diagnostic method for detecting potentially malignant pancreatic lesions with an 88.5% sensitivity; yet it holds a 52.9% specificity and a higher inter-observer variability. Thus, EUS alone has very low diagnosability capacity[5-7]. Similarly, a considerable number of PCLs cannot be characterized by CT, MRI or MRCP alone[8,9]. EUS-guided diagnostics techniques increase EUS accuracy for differentiating PCLs, namely: (1) EUS-FNA; (2) Contrast-enhanced EUS (CE-EUS); (3) Fiberoptic probe cystoscopy (cystoscopy); (4) EUS-guided through-the-needle direct intracystic micro forceps biopsy (mFB); and (5) EUS-guided confocal laser endomicroscopy (nCLE)[9].

EUS-FNA allows biopsy of suspicious lesions and cytological and biochemical cystic fluid analysis [7]. Whereas, CE-EUS help to differentiate between solid *vs* PCLs, by detecting enhanced septa or nodules present within cystic lesions[10]. Through-the-needle fiberoptic probe cystoscopy requires a 19-gauge needle guided by EUS to locate and enter the PCL. Then, the preloaded fiberoptic probe is advanced, allowing visualization of the cyst content as cystic wall features[11]. The microforceps device samples tissue from the cyst's wall, septations, and/or mural nodules and thus increase cellular yield [12]. Furthermore, nCLE characterizes PCLs type by imaging the intact cyst architecture, targeting

abnormal areas and reducing unnecessary sampling of surrounding tissue, with a diagnostic accuracy of 80% to 95%[8].

Given the poor prognosis of malignant pancreatic lesions, determining the best diagnostic approach for early detection of potential malignancy among the variety of newly available EUS-related technology is essential. Therefore, we aimed to compare the accuracy of EUS for detection of potentially malignant PCLs when it is performed alone, EUS-FNA, CE-EUS or cystoscopy and associated with novel EUS-related techniques: mFB and nCLE. We hypothesize that EUS-guided through-the-needle mFB and nCLE may increase malignancy detection during EUS assessment of pancreatic cysts.

MATERIALS AND METHODS

Study design

The following is an observational, analytic, longitudinal, retrospective cohort and single-center study performed at the Instituto Ecuatoriano de Enfermedades Digestivas (IECED), a tertiary center in Ecuador. The study protocol and informed consent documents were approved by the institutional review board, and the study was conducted in accordance with the Declaration of Helsinki. Selected patients signed corresponding informed written consent for healthcare purposes.

Population selection

Records from patients older than 18 years of age who underwent EUS at IECED from January 2013 to March 2018 were extracted from the institutional database. Cases with non-pancreatic lesions were excluded. Patients were allocated to three cohorts: (1) Patients who had been evaluated *via* EUS alone; (2) Patients who had been evaluated with EUS-FNA, CE-EUS and/or cystoscopy; and (3) Those evaluated with novel EUS-related techniques: mFB and nCLE.

Endoscopic techniques malignancy criterion for pancreatic cystic lesions

Due to sparse cellularity of acquired specimens, several complementary clinical, radiological, and imaging techniques are required to achieve PCLs definitive diagnosis. PCLs with potential to progress to malignancy mainly IPMN, mucinous cystic neoplasms (MCN), and neuroendocrine tumors (c-NET) with cystic degeneration. Identifying malignancy features for these lesions with EUS, CE-EUS, cystoscopy, nCLE, FNA, and mFB include the following:

EUS: Presenting two out of the three following characteristics was considered as increased risk for malignancy criteria: main pancreatic duct dilation between 5-9 mm (10 mm high risk stigmata for malignancy), PCLs size > 3 cm, and mural nodules presence[3,13].

CE-EUS: A thick/hyper-enhancing wall/septum, enhancing solid component within a cyst, or an enhancing mural nodule favors malignancy criterion. Furthermore, there is a radiological correlation between pancreatic duct communication and IPMN diagnosis, but not MCN. Also, main duct type IPMNs hold a higher risk of malignancy transformation than branch duct type IPMNs (up to 68% *vs* 22%, respectively). MCN may show peripheral calcifications within multilocular septate lesions[3,14].

Cystoscopy: Cloudy fluid and a smooth cyst wall identify MCN, while finger-like projections and a mucin cloud are perceived with IPMN through single-operator cholangioscopy (SOC)[11,14].

nCLE: Prone to malignancy lesions may depict epithelial or vascular patterns in nCLE[5,8,11,13,15]. nCLE Epithelial patterns: MCN show epithelial borders with a flat mosaic appearance (single or multiple layers of epithelial bands). IPMN exhibit dark rings and papillary projections. c-NET portray a trabecular pattern (fibrous bands separating cells nests). nCLE Vascular patterns: MCN, IPMN and cystic-NET may show a branched pattern; IPMN and MCN may also display a rope-ladder pattern[5].

EUS-FNA and EUS-mFB are resources for tissue sample extraction. For these techniques, cytology should be assessed in the context of radiological and clinical findings[3,11,14]. Low and high-grade IPMN dysplasia should be distinguished as the latter may easily become invasive. Low-grade IPMN: may resemble normal gastric epithelium. High-grade IPMN may show a cell size ≤ 12 μm, hypo/hyperchromasia, background necrosis, nuclear irregularity, large single vacuolated cells, and increased nuclear to cytoplasmic ratio[14].

IPMNs histologic examinations exhibit four possible morphologies: gastric (columnar cells lining papillae with basally located nuclei rich in apical mucin), intestinal (similar morphology to colonic villous adenomas with cigar shaped nuclei and variable apical mucin amount), pancreaticobiliary (more complex papillae composed of rounded nuclei cuboidal cells with some prominent nucleoli), and oncocytic (complex papillae lined with round cells with granular eosinophilic cytoplasm and prominent central nucleoli)[3,14].

MCNs also display low and high-grade dysplasia features. While bland mucin-containing epithelium honeycomb sheets are seen with low-grade MCNs, a complex papillary structure with smooth nuclear contour mucin-containing cells, inconspicuous nucleoli, and fine chromatin is found in high-grade

MCNs. On histologic examination, MCNs show focally flat o cuboidal lining and tall mucin-containing epithelium, with a densely ovarian-type stroma wall that positively stains for progesterone/estrogen receptors, calretinin, and inhibin[3,14].

C-NET aspirate display classic endocrine morphology (pseudorosettes, isolated, and loosely cohesive groups of round/polygonal cells with finely stippled chromatin round nucleus)[5,11,14,15]. Immunostains (chromogranin, CD10, vimectin, and β-catenin cytoplasmic expression) provide a definitive diagnosis[14].

Endoscopic techniques methods

Three experienced endosonographers (C.R-M., J.O., R.V.) performed all EUS evaluations, under general anesthesia with patients in the supine position and use of antibiotic prophylaxis. EUS procedures were performed with a linear-array video echoendoscope (EG-3870 UTK, Pentax Medical, Montalve, NJ, United States) attached to an ultrasound console (HI VISION Avius®, Hitachi Medical Systems, Steinhaus, Switzerland). Indication of EUS-related techniques was based on endosonographers discretion. Although more techniques are available to perform on larger cysts (> 3 cm).

Endoscopic ultrasound fine needle aspiration: EUS-FNA was performed with a 19-gauge needle (Expect™ Slimline, Boston Scientific, Malborough, United States) (Figure 1A). The cystic fluid was examined for tumor markers (amylase, lipase, carcinoembryonic antigen levels).

Contrast enhanced endoscopic ultrasound: To display cystic wall and nodule vascularization, 4.8 mL of SonoVue® (Braccio, Milan, Italy) was used for CE-EUS. Cystic wall and nodule vascularization were defined as visible contrast enhancer bubble movement within the cystic wall, septum, and nodules (Figure 1B), and were referred for further diagnosis with EUS-FNA.

Cystoscopy: Examinations were performed by using a linear-array video echoendoscope attached to an ultrasound console, as previously described. A SOC fiber optic probe (Legacy SpyGlass® fiber optic, Boston Scientific, Marlborough, United States) was inserted through the 19-gauge needle into the cystic cavity to observe the intracystic wall and contents (Figure 1C).

EUS-guided through-the-needle direct intracystic micro forceps biopsy: The target lesion was identified under EUS and punctured with a 19-gauge FNA needle. With the needle inside the lesion, the stylet was removed, and the micro forceps (Moray™ micro forceps, STERIS, Mentor, United States) were inserted through the needle for tissue sampling. Two to three bites of biopsy specimens were taken with each pass of the micro forceps. The tissue acquisition was visually confirmed and directly placed on formalin containers for pathologic evaluation.

EUS-guided confocal laser endomicroscopy: After EUS examination, patients were intravenously injected with 5 mL of 10% fluorescein (BioGlo®, Sofar Productos, Bogota, Colombia) 2 to 3 min before nCLE imaging. CLE was performed using the AQ-Flex nCLE miniprobe (Cellvizio, Mauna Kea Technologies, Paris, France). The probe was advanced through the locking device into the 19-gauge needle. The preloaded needle was advanced under EUS guidance into the PCL. The tip of the nCLE probe was placed in contact with the intracystic epithelium, and intracystic endomicroscopic images were captured (Video 1and Video 2). After image acquisition, the nCLE probe was withdrawn, and the PCL was aspirated.

Data abstraction

Demographic, clinic, endoscopic and histopathological and 24-mo follow-up data were obtained from the institutional database and phone calls when necessary. The study endpoint was to determine agreement between detection of potentially malignant in PCLs (EUS malignancy detection) and malignancy after 24-mo follow-up. EUS malignancy detection was defined based on procedure findings (EUS-alone, CE-EUS, cystoscopy and/or nCLE) reported on endoscopic records, as well as EUS-FNA and/or EUS-mFB aquired biopsy results when available. PCLs were classified as malignant (MCN, IPMN and c-NET) according to Fukuoka criteria. This data was recovered by two endoscopists (C.R.M. and H.P-L.). Malignancy after 24-mo follow-up was based on clinical outcomes, endoscopic surveillance, or surgical specimen histopathology when available. This data was recovered by two general practitioners (R.O. and J.B-B.) and a general surgeon (D.C-L.) who were blinded to information concerning to EUS malignancy detection.

Interobserver agreement

An offline interobserver analysis (IOA) of the EUS criteria (EUS borders, lobularity, wall, microcyst component, diagnosis, and level of confidence) was performed by three endoscopists (J.O., R.V. and J.N.) using a randomly selected EUS image set (n = 111 cases) collected by C.R-M.

Statistical analysis

Technical considerations: Final database was consolidated and encrypted by M.A-M. Data analysis was performed by IECED Institutional Biostatistician (M.P-T.) using R v.4.0 (R Foundation for Statistical

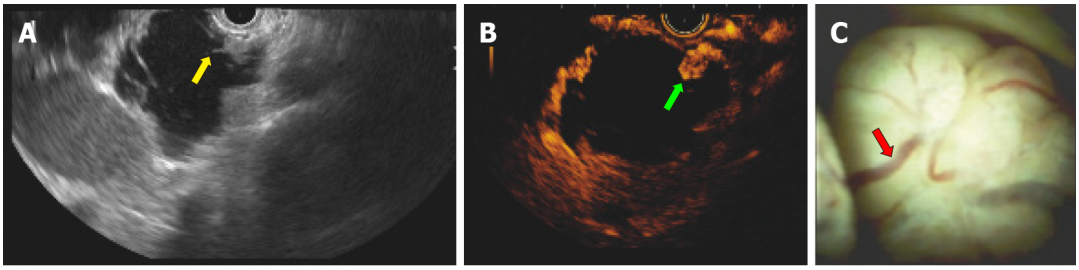

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Figure 1 Case No. 13: A 77 years old woman with a pancreatic cyst lesion corresponding to an intraductal papillary mucinous neoplasm. The lesion exhibited malignancy criteria at endoscopic ultrasound (EUS) and related techniques. A: EUS identifying a 4 cm pancreatic cyst lesion with mural nodules (yellow arrow); B: Mural nodule with hyper-enhancing at EUS (green arrow) shown in contrast-enhanced EUS; C: EUS-guided cystoscopy using a digital probe showing vascularity (red arrow) of a pancreatic macrocystic lesion filled with clear fluid.

Computing, Vienna, Austria). A *P*-value <0.05 was considered statistically significant.

Sample size calculation: We considered a 100% specificity of EUS + nCLE for the prediction of potentially malignant PCLs, with a 35% disease prevalence (6/31 mucinous cystic neoplasm and 5/31 IPMNs) for defining the sample size (16). We estimated a sample size of 25 patients for each cohort, with an α and β-error of 5% and 20% respectively, and an 80% statistical power.

Descriptive analysis: Numeric variables were described through the mean ± SD or median (minimum-maximun range) in accordance with statistical distribution (Kolmógorov-Smirnov test). Categorical variables were described with frequency (%), and 95%CI when corresponding. Descriptions about techniques combination was summarized on a Venn Diagram (17).

Inferential analysis: Observed agreement between EUS malignancy detection and malignancy after 24-mo follow-up was established. The statistical association between EUS alone or EUS with an additional endoscopic technique *vs* the positive observed agreement described above was determined by binary logistic regression [odds ratio (OR)]. A univariate analysis was performed for each individual technique. Those with a significant association were entered into the multivariate analysis. The overall diagnostic accuracy for malignancy detection was determined for each diagnostic procedure which shown significance on multivariate analysis, considering a 24-mo follow-up as gold standard. Overall diagnostic accuracy comprehended calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio, and observed agreement. For multivariate analysis discrimination, we estimated the corresponding area under the receiver operating characteristics (AUROC) curves and contrasting using the DeLong's test for two ROC curves. The IOA of the EUS criteria was performed using Fleiss' kappa score (κ) calculation and interpreted based on Landis and Koch criteria.

RESULTS

Patient selection

A total of 2812 patients were referred to our unit for diagnostic EUS along study period. Of these, 856 had pancreatic lesions, of which 129 patients with PCLs were included for analysis (n = 129) (Figure 2).

Baseline characteristics

The median age of the 129 patients with PCLs was 69 years, and 69.8% patients were female. The most frequent pancreatic cyst location was the head of the pancreas (35.7%). Younger patients were significantly evaluated with EUS and an additional novel technique (mFB and/or nCLE) in comparison to those evaluated with EUS alone, EUS-FNA, CE-EUS or cystoscopy (P < 0.001). Cysts size above 30 mm were reported among patients evaluated with EUS and an additional novel technique (46.3%) compared with general cohort (27.1%; P < 0.001). There were no statistically significant differences when comparing gender and PCLs location between patients evaluated with EUS alone and those evaluated with EUS plus additional diagnostic techniques (Table 1).

EUS was performed with an additional diagnostic technique in 82/129 patients: EUS-FNA [21/82 (25.6%)], CE-EUS [20/82 (24.4%)], cystoscopy [27/82 (32.9%)], mFB [36/82 (43.9%)], and nCLE [44/82 (53.7%)]. More than one diagnostic technique was performed in a sample proportion (Figure 3). A 100% technical success was reached, with no documented adverse events for any of the performed procedures.

Table 1 Baseline characteristics and clinical 24-mo follow-up outcome of included patients

	Total (*n* = 129)	EUS alone (*n* = 47)	EUS + FNA/CE/ Cystoscopy (*n* = 28)	EUS + mFB/nCLE (novel techniques) (*n* = 54)	*P* value
Age (yr), median (range)	69 (26-97)	71 (29-97)	78 (49-92)	59 (27-97)	< 0.001[a]
Sex (female), *n* (%)	90 (69.8)	33 (70.2)	19 (67.0)	38 (70.4)	0.9694[b]
Pancreatic cyst location, *n* (%)					0.6258[b]
Uncinate process	3 (2.3)			3 (5.6)	
Head	46 (35.7)	17 (36.2)	9 (32.1)	20 (37.0)	
Neck	13 (10.1)	3 (6.4)	4 (14.3)	6 (11.1)	
Body	36 (27.9)	14 (29.8)	8 (28.6)	14 (25.9)	
Tail	31 (24.0)	13 (27.7)	7 (25.20)	11 (20.4)	
Cyst size (mm), *n* (%)					
< 10 mm	33 (25.6)	29 (61.7)	1 (3.6)	3 (5.6)	< 0.001[b]
10-30 mm	61 (47.3)	16 (34.0)	19 (67.9)	26 (48.1)	
> 30 mm	35 (27.1)	2 (4.3)	8 (28.6)	25 (46.3)	
Additional endoscopic procedure used for diagnosis[1], *n* (%)					-
EUS-FNA	21 (16.3)		17 (60.7)	4 (7.4)	
CE-EUS	20 (15.5)		11 (39.3)	9 (16.7)	
Cystoscopy	27 (20.9)		1 (3.6)	26 (48.1)	
mFB	36 (27.9)			36 (66.7)	
nCLE	44 (34.1)			44 (81.5)	
Pancreatic cyst diagnosis, *n* (%)					< 0.001[b]
Malignant[2]	81 (62.8)	46 (97.9)	19 (67.9)	16 (29.6)	
Mucinous cystadenocarcinoma	6 (4.7)	1 (2.1)	4 (14.3)	1 (1.9)	
Mucinous cystadenoma	4 (3.1)		1 (3.6)	3 (5.6)	
Intraductal papillary mucinous neoplasm	70 (54.3)	45 (95.7)	14 (50.0)	11 (20.4)	
Neuroendocrine	1 (0.8)			1 (1.9)	
Non-malignant[2]	48 (37.2)	1 (2.1)	9 (32.1)	38 (70.4)	
Serous cystadenoma	46 (35.7)	1 (2.1)	9 (32.1)	36 (66.7)	
Pseudocysts	2 (1.6)			2 (3.7)	
24-mo follow-up, *n* (%)					0.0351[b]
Malignant	28 (21.7)	7 (14.9)	11 (39.3)	10 (18.5)	
Non-malignant	101 (78.3)	40 (85.1)	17 (60.7)	44 (81.5)	
Positive observed agreement between EUS-guided biopsy *vs* 24-mo follow-up for malignancy detection, *n* (%)	70 (54.3)	8 (17.0)	18 (64.3)	44 (81.5)	< 0.001[b]

[a]Kruskal-Wallis rank sum test.
[b]Pearson's Chi-squared test.
[1]Additional endoscopic procedures are not mutually exclusive.
[2]Cases with histopathological confirmation met the Fukuoka criteria.
EUS: Endoscopic ultrasound; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration; Cystoscopy: Fiberoptic probe cystoscopy; nCLE: Endoscopic ultrasound-guided needle-based confocal laser-endomicroscopy; mFB: Endoscopic ultrasound-guided through-the-needle direct intracystic micro forceps biopsy; CE-EUS: Contrast-enhanced endoscopic ultrasound.

According to the PCLs EUS findings and guided biopsy when available (*n* = 53), potentially malignant PCLs were detected in 81/129 (62.8%) patients, and the most frequent lesion among this group was IPMN [70/129 (54.3%)]. In the nonmalignant group [48/129 (37.2%)], 46 cases were serous cystadenomas (Table 1). Observed agreement between EUS malignancy detection and malignancy after

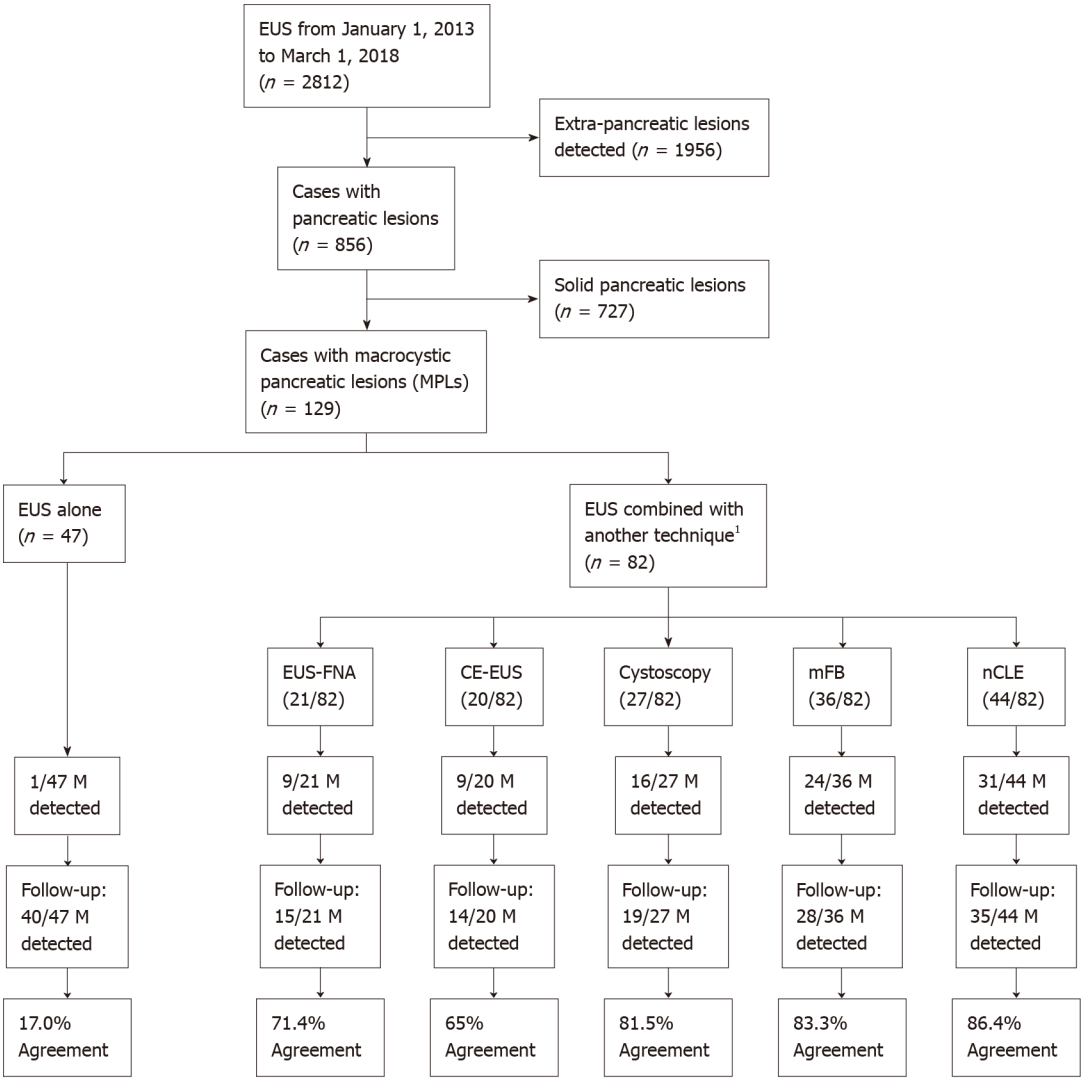

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Figure 2 Population study flowchart. [1]Numbers of techniques were not mutually exclusive. Endoscopic ultrasound could be combined with more than one other technique, as shown on the illustrated Venn diagram in Figure 3. EUS: Endoscopic ultrasound; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration; Cystoscopy: Fiberoptic probe cystoscopy; nCLE: Endoscopic ultrasound-guided needle-based confocal laser-endomicroscopy; mFB: Endoscopic ultrasound-guided through-the-needle direct intracystic micro forceps biopsy; CE-EUS: Contrast-enhanced endoscopic ultrasound; M: Malignancy.

24-mo follow-up was higher in patients evaluated with EUS plus at least one additional novel technique (mFB and/or nCLE), followed by EUS-FNA, CE-EUS and or cystoscopy; than in patients evaluated with EUS alone [42/55 (80.0%) *vs* 18/27 (66.7%) *vs* 8/47 (17%), respectively; OR 4.35, 95%CI: 2.70-7.37; $P < 0.001$].

Univariable and multivariable analysis

Independently, there was a positive statistical association and observed agreement for EUS malignancy detection with cystoscopy, mFB or nCLE, and 24-mo follow-up. EUS-FNA and CE-EUS exhibited a positive but nonsignificant association; whereas EUS alone only presented a negative significantly association [OR 0.066 (0.025-0.157; $P < 0.001$)] when considering the agreement between EUS malignancy detection and malignancy after 24-mo follow-up as an outcome.

Through multivariate analysis, we confirmed that malignancy detection was significantly more accurate with nCLE [OR 8.441 (2.698-33.081; $P < 0.001$)] and mFB [OR 3.425 (1.104-11.682; $P = 0.038$)] than cystoscopy [OR 0.622 (0.125-2.813; $P = 0.541$)] (Table 2).

Diagnostic accuracy for determining malignancy

EUS alone was performed in 47 cases and had a sensitivity, specificity, PPV, and NPV of 100%, 3%, 15%, and 100%, respectively. EUS-FNA, CE-EUS, and/or cystoscopy was performed in 28 cases and had a sensitivity, specificity, PPV, and NPV of 91%, 47% 53% and 89%, respectively. EUS with nCLE and mFB yielded similar results for sensitivity (89% *vs* 88%), specificity (86% *vs* 82%), PPV (62% *vs* 58%) and NPV (97% *vs* 96%). When the three techniques were simultaneously performed (EUS with nCLE and mFB, *n*

Table 2 Association between different additional performed techniques *vs* a positive observed agreement for malignancy diagnosis among endoscopic ultrasound and endoscopic ultrasound-related techniques *vs* 24-mo follow-up [OR (95%CI; *P* value)]

	Univariate analysis[1]	Multivariate analysis[1]
EUS alone (*n* = 47)	0.066 (0.025-0.157; < 0.001)	
EUS-FNA (*n* = 21)	2.409 (0.905-7.182; 0.091)	
CE-EUS (*n* = 20)	1.694 (0.642-4.811; 0.298)	
Cystoscopy (*n* = 27)	4.950 (1.862-15.695; 0.003)	0.622 (0.125-2.813; 0.541)
mFB (*n* = 36)	6.625 (2.667-19.024; < 0.001)	3.425 (1.104-11.682; 0.038)
nCLE (*n* = 44)	10.489 (4.242-30.125; < 0.001)	8.441 (2.698-33.081; < 0.001)

[1]Positive observed agreement: In 70/129 (54.3%) there was a positive agreement between endoscopic ultrasound *vs* 24-mo follow-up for a malignant and non-malignant diagnosis.

EUS: Endoscopic ultrasound; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration; Cystoscopy: Fiberoptic probe cystoscopy; nCLE: Endoscopic ultrasound-guided needle-based confocal laser-endomicroscopy; mFB: Endoscopic ultrasound-guided through-the-needle direct intracystic micro forceps biopsy; CE-EUS: Contrast-enhanced endoscopic ultrasound.

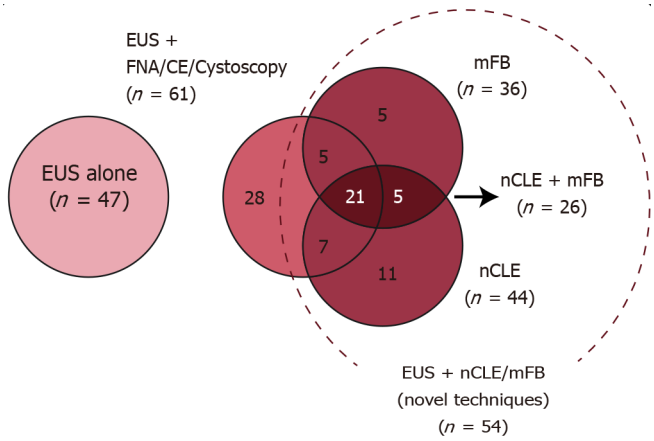

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Figure 3 Venn diagram describing distribution of additional diagnostic techniques performed in the studied population. EUS: Endoscopic ultrasound; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration; Cystoscopy: Fiberoptic probe cystoscopy; nCLE: Endoscopic ultrasound-guided needle-based confocal laser-endomicroscopy; mFB: Endoscopic ultrasound-guided through-the-needle direct intracystic micro forceps biopsy; CE-EUS: Contrast-enhanced endoscopic ultrasound.

= 26), the diagnostic accuracy analysis showed that the sensitivity, specificity, PPV, and NPV were 100%, 89%, 78%, and 100%, respectively. MCC identified a good correlation between EUS malignancy detection and malignancy after the 24-mo follow-up through different techniques. Nonetheless, EUS paired with nCLE and mFB showed the highest agreement (MCC = 0.83) (Table 3).

Detection of potentially malignant PCLs using EUS alone reached a 51.3% AUROC (P = 0.3599; moderate agreement). Meanwhile, EUS-guided mFB, nCLE or/and mFB reached an 87.3% AUROC (P < 0.001), 84.8% (P < 0.001) and 94.7% (P < 0.001), respectively. In addition, nCLE reached a greater AUROC in comparison to EUS alone (P < 0.001) (Figure 4A). Moreover, a significantly higher AUROC was described for combined EUS-guided nCLE and mFB in comparison to EUS-FNA/CE-EUS/cystoscopy (94.7% *vs* 69%, P = 0.044) (Figure 4B).

Interobserver agreement

In the secondary IOA performed by three experienced endoscopists, the κ values in EUS borders, lobularity, wall, microcyst component, diagnosis, and level of confidence were as follows: 0.12 (poor agreement), 0.08 (poor agreement), 0.04 (poor agreement), 0.29 (fair agreement), 0.21 (fair agreement), and 0.06 (poor agreement) respectively.

Table 3 Overall diagnostic accuracy for determining malignancy [% (95%CI)]

	EUS alone (*n* = 47)	EUS + FNA/CE/ Cystoscopy (*n* = 28)	EUS + mFB (*n* = 36)	EUS + nCLE (*n* = 44)	EUS + nCLE + mFB (*n* = 26)
Sensitivity	7/7; 100.0% (59.3-100.0)	10/11; 90.9% (58.7-99.8)	7/8; 87.5% (47.3-99.7)	8/9; 88.8%; (51.8-99.7)	7/7; 100.0% (59.0-100.0)
Specificity	1/40; 2.5% (0.1-13.2)	8/17; 47.1% (22.9-72.3)	23/28; 82.1% (63.1-93.9)	30/35; 85.7% (69.7-95.2)	17/19; 89.4% (66.9-98.7)
PPV	7/46; 15.2% (6.3-28.9)	10/19; 52.6% (28.9-75.6)	7/12; 58.3% (27.7-84.8)	8/13; 61.5% (31.6-86.1)	7/9; 77.8% (40.0-97.1)
NPV	1/1; 100.0% (2.5-100.0)	8/9; 88.9% (51.8-99.7)	23/24; 95.8% (78.9-99.8)	30/31; 97% (83-100)	17/17; 100.0% (80.5-100.0)
PLR	1.03 (0.98-1.08)	1.72 (1.06-2.79)	4.90 (2.12-11.31)	6.22 (2.68-14.47)	9.50 (2.56-35.24)
NLR	n/a	0.19 (0.03-1.34)	0.15 (0.02-0.96)	0.13 (0.02-0.83)	n/a
Observed agreement	8/47 (17%); *P* = 0.672[a]	18/28 (64.3%); *P* = 0.049[a]	30/36 (83.3%); *P* < 0.001[a]	38/44 (86.4%); *P* < 0.001[a]	24/26 (92.3%); *P* < 0.001[a]
MCC	+ 0.06	+ 0.40	+ 0.61	+ 0.66	+ 0.83
AU-ROC	51.3%; *P* = 0.359[b]	69.0%; *P* = 0.02[b]	84.8%; *P* < 0.001[b]	87.3%; *P* < 0.001[b]	94.7%; *P* < 0.001[b]

[a]Fisher's exact test for count data.
[b]Mann–Whitney U test.
EUS: Endoscopic ultrasound; nCLE: Confocal laser endomicroscopy; mFB: Endoscopic ultrasound-guided through-the-needle direct intracystic micro forceps biopsy; PPV: Positive predictive value; NPV: Negative predictive value; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; MCC: Matthews correlation coefficient; AU-ROC: Area under the receiver operating characteristics curve; n/a: Not available.

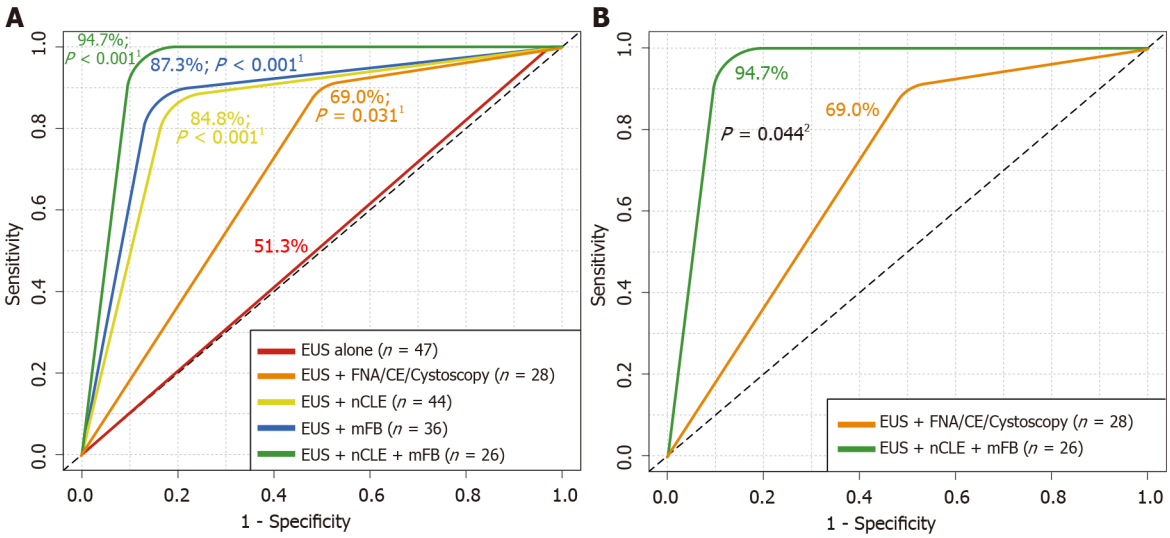

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Figure 4 Received operating characteristics describing overall diagnostic accuracy of endoscopic ultrasound alone and in addition with fine needle aspiration or contrast-enhanced endoscopic ultrasound, needle-based confocal laser-endomicroscopy and/or with direct intracystic micro forceps biopsy for detecting malignancy. A: Comparison among endoscopic ultrasound (EUS) alone *vs* additional diagnostic techniques; B: Comparison among EUS alone *vs* EUS + EUS-guided needle-based confocal laser-endomicroscopy (nCLE) + EUS-guided through-the-needle direct intracystic micro forceps biopsy (mFB). [1]DeLong's test for two received operating characteristics (ROC) curves comparing EUS-alone area under the ROC curve (red line) with EUS + fine needle aspiration (FNA)/contrast-enhanced (CE) (orange line), EUS + nCLE (yellow line), EUS + mFB (blue line) and EUS + nCLE + mFB (green line). [2]DeLong's test for two ROC curves comparing EUS + FNA/CE (orange line) with EUS + nCLE + mFB (green line). EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; Cystoscopy: Fiberoptic probe cystoscopy; nCLE: Endoscopic ultrasound-guided needle-based confocal laser-endomicroscopy; mFB: Endoscopic ultrasound-guided through-the-needle direct intracystic micro forceps biopsy; CE: Contrast-enhanced.

DISCUSSION

Various clinically-available advanced EUS-guided diagnostic techniques have improved the accuracy of malignancy detection among PCLs; however, these techniques are not referenced in current guidelines, with unsatisfactory diagnostic accuracy in the risk stratification of potentially malignant PCLs[4].

To provide guidance on the relative accuracy and effectiveness of these new EUS-related techniques, we compared various additional endoscopic techniques during the EUS evaluation of PCLs. We evaluated the accuracy of EUS alone with more recent EUS-related techniques, namely EUS-FNA, cystoscopy, nCLE, mFB, and CE-EUS and found that the highest level of malignancy detection can be achieved when EUS is combined with both nCLE and direct intracystic mFB.

An increasing number of PCLs have been identified due to the growing use of complementary diagnostic techniques, such as CT and MRI; moreover, the malignancy potential of PCLs vary, and current diagnostic techniques cannot characterize the lesions with precision by their self[18-20]. Due to the malignancy potential, patients with pancreatic neoplasms are recommended to undergo resection therapy; however, for patients with a high risk of postsurgical complications, preoperative determination of malignancy is critical for management guidance.

In our study, EUS alone had a low agreement in comparison to the 24-mo follow-up. Also, in an offline interobserver agreement between three endosonographers, endoscopic criteria showed low agreement between operators, as previously described. Therefore, EUS itself should be complemented with additional endoscopic techniques for a more accurate detection of malignancy in PCLs.

Wang *et al*[21] demonstrated that EUS-FNA can accurately confirm the presence of malignancy but does not perform well at excluding malignant or premalignant pancreatic lesions. This procedure achieved a pooled sensitivity and specificity of 51%, 94%, respectively, for differentiating malignant lesions. In our study, which included 21/129 patients with pancreatic lesions for whom FNA was performed, we found that EUS-FNA did not achieve statistical significance in detecting malignancy with a modest agreement with the 24-mo follow-up; however, this may be due a limited number of cases in our cohort.

The DETECT trial revealed that a combination of through-the-needle cystoscopy and nCLE for PCLs under EUS was feasible, with a sensitivity of 90% for cystoscopy in the clinical diagnosis of MCNs, an 80%sensitivity for nCLE, and a 100% sensitivity for the combination of both[11]. In our study, we analyzed both techniques (separately and then combined) and obtained similar results – we obtained a sensitivity of 89% for EUS-guided-nCLE and 88% for EUS-guided through-the-needle cystoscopy; however, the sensitivity of EUS-guided nCLE combined with mFB was 78%. Additionally, in our cohort, we had more heterogenic lesions than in the DETECT trial, which was limited to mucinous lesions.

Haghighi *et al*[8] compared the diagnostic accuracy of nCLE and EUS-FNA, where nCLE was found to have a higher accuracy (87.5%), sensitivity (91.7%), and NPV (93.3%). In our cohort, 44/129 patients underwent nCLE, obtaining similar results (an 86.0% accuracy, an 89% sensitivity, and an NPV of 96%). Konda *et al*[22] reviewed 31 PCLs that were examined using nCLE, and showed a high specificity (100%) and PPV (100%); and an overall accuracy of 71%. In our study, we obtained a higher sensitivity (89%), NPV (96%) and accuracy (86%) probably owing to a higher number of cases.

EUS-nCLE and mFB exhibited an 86.4% and an 83.3% agreement for PCLs malignancy detection, probably due to a better *in vivo* cyst component evaluation and guided tissue acquisition. EUS combined with nCLE and mFB reached the highest AUROC (94.7%), in comparison to independent nCLE (87.3%) and mFB (84.8%). We propose that these techniques should be considered for the diagnostic workup of PCLs.

The main limitation of our study lies in its retrospective design and in establishing an agreement of different endoscopic techniques for determining potential malignancy among different types of PCLs. This resulted in a difficulty in the recovery of different size cysts, where the smaller the cyst, the fewer the diagnostic methods at our disposal for use. On the other hand, larger cysts (specially over 30 mm), allowed us to perform a wider array of diagnostic procedures, including novel techniques. Moreover, these novel endoscopic techniques (*i.e,* nCLE), are costly, limiting their widespread use. Furthermore, these tools require training, which increase the procedure's startup cost. Despite these limitations, we compared these endoscopic techniques in terms of their ability to detect potential malignancy in patients with PCLs, and not only pancreatic lesions, as with other studies. Finally, as this study was designed in the context of PCLs assessment with EUS, to estimate EUS (and eventual used related techniques) diagnosability of malignancy considering a 24-mo follow-up as gold standard, a prospective diagnostic trial to re-analyse histopathological samples of PCLs after discarding malignancy during follow-up may be warranted to further asses the accuracy in diagnosing high-grade dysplasia/adenocarcinoma in non-malignant PCLs (MCN, IPMN) using the studied endoscopic techniques.

CONCLUSION

In conclusion, new EUS technologies such as through-the-needle techniques (direct intracystic mFB combined with nCLE), improve malignancy detection in patients with PCLs. However, multicenter, and cost-benefit studies are recommended to validate these findings.

ARTICLE HIGHLIGHTS

Research background

Pancreatic cystic lesions (PCLs) incidence is rising mainly in elderly patients. Accurate diagnosing and appropriate management of patients with malignant PCLs, have a positive impact in regards of healthcare expenses and in patients' quality of life.

Research motivation

Currently, there is insufficient data about the accuracy in the diagnosing of PCLs, especially with novel endoscopic techniques. Furthermore, the early detection of potentially malignant PCLs, increases the possibility of a curative approach in said patients.

Research objectives

Given the poor prognosis of malignant PCLs, attaining early detection, an accurate diagnosis, and determining the best diagnostic approach with newly available endoscopic techniques, was essential to this study.

Research methods

This was a retrospective, single-center study. Patients were allocated to three evaluation cohorts: (1) Endoscopic ultrasound (EUS) alone; (2) EUS- fine needle aspiration, contrast-enhanced-EUS and/or EUS-guided fiberoptic probe cystoscopy (cystoscopy); and (3) EUS-guided direct intracystic micro-forceps biopsy (mFB) and EUS-guided needle-based confocal laser-endomicroscopy (nCLE); and compared the accuracy of these techniques for the detection of potentially malignant PCLs.

Research results

We described that pairing EUS, mFB, and nCLE, had a statistically significant improved detection of potentially malignant PCLs compared to any of the evaluated techniques alone. No adverse events were documented, and a 100% technical success rate was achieved.

Research conclusions

In our study, EUS-guided mFB combined with nCLE, improve malignancy detection in patients with PCLs.

Research perspectives

To define formal diagnostic and therapeutical guidelines, we encourage researchers to conduct long-term follow-up randomized multicenter and cost-benefit studies, comparing newly available endoscopic techniques for the assessment of PCLs.

FOOTNOTES

Author contributions: Robles-Medranda C contributed to study conception, design, drafting; Olmos JI, Del Valle Zavala R, Nebel JA, Calle Loffredo D and Pitanga-Lukashok H contributed to study design, acquisition of data; Puga-Tejada M and Oleas R contributed to study design; Baquerizo-Burgos J, Puga-Tejada M and Oleas R contributed to study drafting, acquisition/analysis of data; Arevalo-Mora M did final database study consolidation and encryption, data acquisition; Robles-Medranda C, Olmos JI, Del Valle Zavala R, Nebel JA, Calle Loffredo D, Pitanga-Lukashok H, Puga-Tejada M, Oleas R and Arevalo-Mora M contributed to critical revision of important intellectual content; all authors did final approval of the version to be published.

Institutional review board statement: The study was approved by the Institutional Review Board of Instituto Ecuatoriano de Enfermedades Digestivas.

Informed consent statement: All study participants, and their legal guardians, provided informed written consent prior to study enrolment.

Conflict-of-interest statement: Robles-Medranda C reports other from Pentax Medical, other from Boston Scientific, other from Steris, other from Medtronic, other from Motus, other from Micro-tech, other from G-Tech Medical Supply, other from CREO Medical, other from Mdconsgroup, outside the submitted work; The other authors declare no conflicts of interest.

Data sharing statement: The data that support the findings of this study are openly available by contacting the corresponding author.

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ORIGINAL ARTICLE

Observational Study

Ergonomics of gastrointestinal endoscopies: Musculoskeletal injury among endoscopy physicians, nurses, and technicians

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Abstract

BACKGROUND

Musculoskeletal injuries (MSI) have plagued endoscopists and ancillary staff for decades without any innovative and strong ergonomic guidelines. It has placed a physical and mental strain on our endoscopists and ancillary staff. We have very have limited data supporting this claim in our region and most data is supported by western literature.

AIM

To document the prevalence of MSI, and awareness and practices of ergonomics by endoscopists and ancillary staff.

METHODS

This is an observational cross-sectional study, conducted in Karachi, a city that boasts the maximum number of daily endoscopies in the country. An eleven-point self-administered questionnaire was distributed and used to evaluate MSI and ergonomic adjustments amongst three tertiary care setups in Karachi. An onsite survey *via* a 13-point checklist for endoscopy suite facilities was used to assess the ergonomically friendly conveniences at five tertiary care setups in Karachi. A total of 56 participants replied with a filled survey.

RESULTS

There were 56 participants in total with 39 (69.6%) males. Pain and numbness were documented by 75% of the patients, with pain in the neck (41.1%), lower back (32.1%), shoulder (21.4%), thumb (12.5%), hand (23.2%), elbow (8.9%), and carpal tunnel syndrome (CTS) (7.1%). Of those, 33.3% attributed their symptoms

to endoscopy, 14.2% said that symptoms were not caused by endoscopy, and 52.4% were not certain whether endoscopy had caused their symptoms. Twenty-one point four percent of patients had to take time off their work, while 33.9% took medications for pain. Ergonomic modifications to prevent musculoskeletal injury, including placement of endoscopic monitor at eye level and the cardiac monitor in front, stopping the procedure to move patients, sitting while performing colonoscopy, and navigating height-adjustable bed were used by 21.4%. Nine out of 13 ergonomic facilities were not present in all five tertiary care hospitals. Conveniences, such as anti-fatigue mats, height-adjustable computer stations, and time out between patients were not present.

CONCLUSION
Three-fourth of our endoscopists reported MSI, of which more than half were not sure or attributed this problem to endoscopy. The prevalence of MSI warrants urgent attention.

Key Words: Endoscopy; Ergonomics; Injury; Musculoskeletal; Endoscopists; Gastroenterologist

Core Tip: Musculoskeletal injuries (MSI) have impacted gastroenterologists and ancillary staff involved in endoscopy. Maneuvers, time duration, and failure of ergonomic practices and provision of facilities have led to the prevalence of MSI. This has resulted in stress, chronic pain management, office leaves, and consumption of analgesics. We found three-fourth of our endoscopists reported MSI, of which more than half were not sure or attributed this problem to endoscopy. The high prevalence of MSI and lack of awareness among endoscopists and ancillary staff needs to be addressed urgently.

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INTRODUCTION

Several studies have suggested a high prevalence of musculoskeletal injuries (MSI) among endoscopists and ancillary staff. Survey-based studies estimate a 29% to 89% prevalence of musculoskeletal pain among gastroenterologists[1], which directly translates to a loss of productivity. Rigorous training and increased demand for endoscopies make a gastroenterologist an asset in the workplace, especially in the developing world. A work-related injury can greatly affect the quality and longevity of the gastroenterologist, which can ultimately exacerbate the shortage of specialists[2]. Improving ergonomic conditions will ensure maximum utilization of this scarce human resource. MSI are widespread and are strongly correlated with high procedure volume and procedure duration[3]. Endoscopists are at risk for overuse syndromes and overuse injuries, such as carpal tunnel syndrome (CTS), De Quervain's tenosynovitis, and lateral epicondylitis because of the repetitive movements, pinching and gripping of the endoscope, pushing, pulling, torquing of the insertion tube and potentially awkward posture associated with endoscopic procedures[1,3]. However, institutional changes minimizing MSI are limited, which can be an important contributory factor of lack of awareness[1].

Limited documented data, especially in the eastern population, and lack of awareness are contributory factors to the lack of widespread change. Additionally, a robust analysis to identify risk factors associated with endoscopy-related injury is lacking. Creating awareness about the importance of ergonomics in endoscopy may prevent future injury. There is no standardized curriculum for learning endoscopic techniques, and most endoscopists learn their skills during their fellowship training through their faculty mentor, which creates great variability in the level of skill among trainees. This variability and lack of emphasis on ergonomics during teaching propagate the risk of MSI. Strategies for the management of the risk of MSI related to the practice of endoscopy include compliance with currently recommended ergonomic practices, standardized education of trainees in ergonomic technique when practicing endoscopy, research toward the modification and development of more ergonomic endoscopes and procedure spaces, and institutional emphasis[4]. This study aims to document the prevalence of MSI, awareness and practice of ergonomics by endoscopists and ancillary staff.

MATERIALS AND METHODS

Questionnaires were tendered to endoscopists and ancillary staff. The questionnaire was designed and informed consent was implied by a completed response to the survey. The survey was handed out following June 2019 onwards with a collection on follow-up from respondents. Ethical approval was obtained from Ethics Review Committee Aga Khan University (5357-Med-ERC-18).

Study subjects

Participants were endoscopists and ancillary staff found in the endoscopy suites in three tertiary care hospitals namely, Aga Khan University Hospital, Liaquat National Hospital, and Dr. Ruth K. M. Pfau Civil Hospital, all located in Karachi, Pakistan. All endoscopy physicians, nurses, and technicians approached. There was no monetary compensation for participation.

Evaluation of MSI

An eleven-point, self-administered, paper-based survey was devised by an endoscopist and a member of the ancillary staff (Supplementary Material 1). Items in the questionnaire were generated based on literature review[2,3,5] and multidisciplinary discussions on the topic. These questions focused on demographics, average physical activity, location of the injury. It also questioned the subject's perception of work/endoscopy-related MSI, and further intrigued on their remedies, the need for skipping work, and the use of ergonomic techniques to facilitate themselves.

Initially, the survey was pilot-tested by handing it over to endoscopists and ancillary staff members from the Department of Gastroenterology at Aga Khan University Hospital. The purpose was to evaluate its language, content clarity, and to deduce an approximate time to complete, although trained researchers were present during data collection to clarify any ambiguities. The final survey evaluated the respondent's general demographic, characteristics, workload, type, treatment, and impact of severity of MSI on a daily professional capacity. The survey took approximately 6 min to be filled out.

Assessment of facilities to prevent MSI

A 13-point checklist (Supplementary Material 2) was adapted and devised from a literature search[6-9]. The endoscopic suites at five tertiary care hospitals, namely, Aga Khan University Hospital, Ziauddin University Hospital, Liaquat National Hospital, Dr. Ruth K. M. Pfau Civil Hospital, Sindh Institute of Urology and Transplant, all placed within Karachi, Pakistan were evaluated. The checklist was used to assess measures employed by these 5 major tertiary care hospitals in this metropolis to reduce MSI.

Ergonomic conditions were evaluated by the investigators. These 13 points briefly assessed the suite for endoscopic monitor, monitor height adjustability, booms, and stands. It also assessed time out between two consecutive patients, support stands, anti-fatigue mats, tiltable examination beds, cardiac monitor adjustability, and having the endoscopic retrograde cholangiopancreatography (ERCP) room in the same suite (Supplementary Material 2).

Statistical analysis

This observational cross-sectional study had its statistical review performed by a biomedical statistician present at the Department of Medicine at Aga Khan University. Analysis was performed using SPSS (Statistical Package of Social Sciences) version 19. Continuous variables were reported as mean ± SD. Prevalence (%) of demographic and clinical factors were assessed. All participants were divided into four groups: endoscopists, trainees, nurses, and technicians, and had their frequency of MSI compared in different groups by chi-square test. This data was stratified by gender and evaluated. All *P* values were based on two-sided tests and significance was set at a *P* value less than 0.05.

RESULTS

Demographics

Data from 56 participants were collected, of which 39 (69.6%) were male (Table 1). Eighty-seven point five percent had right-hand dominance. There were 23.2% endoscopists, 16.1% gastroenterology residents, 26.8% endoscopy nurses, and 33.9% endoscopy technicians.

The level of physical activity was appraised. No regular exercise was seen in 41.1%, 23.2% exercised less than 150 min/wk, 8.9% exercised 150 min/wk, and 26.8% exercised more than 150 min/wk.

MSI

Participants who had been doing endoscopies for up to 5 years accounted for 48.9%, while 51% had been involved in endoscopy for more than 5 years.

Pain and numbness were reported by 75% of total respondents with anatomical regions specified as neck (41.1%) lower back pain (32.1%) shoulder pain (21.4%), thumb pain (12.5%) hand pain (23.2%), elbow pain (8.9%) and CTS (7.1%), being the most affected with pain (Figure 1).

Table 1 Demographics

Demographics	*n* = 56 (%)
Mean age, yr	35.09 (18-62)
Male	39 (69.6)
Female	17 (30.3)
Endoscopist	13 (23.2)
GI resident	9 (16.1)
Endoscopy nurse	15 (26.8)
Endoscopy technician	19 (33.9)
Mean number of endoscopies performed per week	63.85

Table 1 shows the demographic representation of our respondents out of n = 56. We stratified our data based on gender and profession to analyze musculoskeletal injuries. GI: Gastrointestinal.

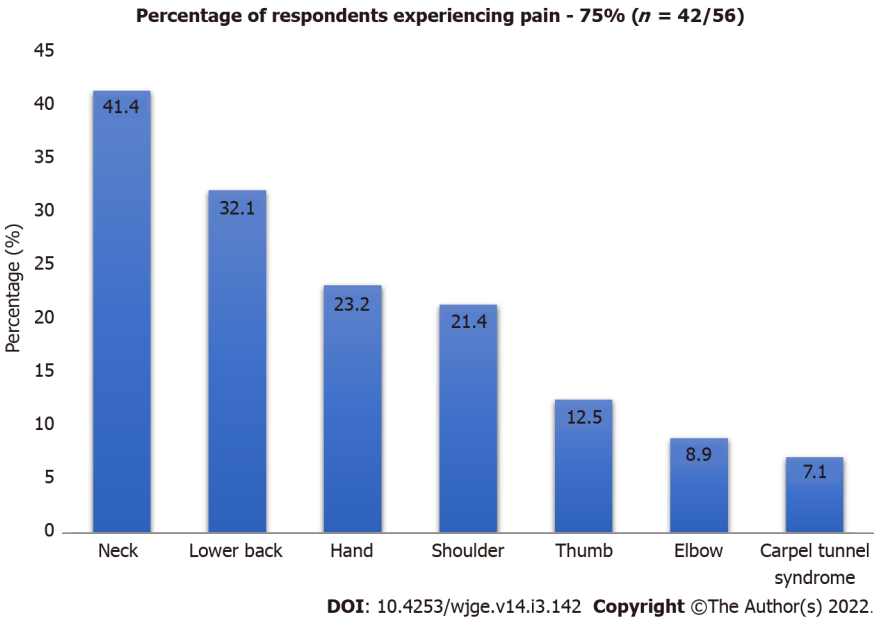

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Figure 1 The percentage of respondents experiencing a particular type of pain.

On an individual basis, out of endoscopists, residents, nurses, and technicians, we found endoscopists reporting the least to experience pain (53.8%) (Table 2). This was followed by residents at 77.8%, technicians at 78.9%, and finally with nurses reporting the most pain at 86.7%. Overall, there is not much distribution amongst the subgroups of the endoscopy team; however, we saw four cases of CTS. All four belonged to endoscopy nurses or endoscopy technicians.

We found a majority of the male and female technicians (66% and 100%) (Table 3) agreeing to neck pain which is the most common area affected overall while most nurses, both in males (100%) and females (53.8%) said to experience no pain in their neck. This does have real-time value as we found nurses using and performing hand and wrist-based actions and movements more frequently, and likewise, the nurses in our setup play a major role in holding the mouth guard. Table 3 can be seen showing a sub-analysis of gender-based data of male *vs* females in their respective professions of endoscopists, residents, nurses, and technicians.

Of all the total respondents only 33.3% of those having pain attributed it to endoscopy while, 52.4% were not certain whether the symptoms had been caused by endoscopy and 14.3% said that symptoms were not caused by endoscopy.

Thirty-two point one percent of respondents indicated evident pain during endoscopy, with 33.3% of those were bothered by this symptom.

Thirty point five percent of the participants indicated that the duration of their symptoms was more than 6 mo, and of those, 57.1% indicated that their symptoms were static and 10.7% indicated they were increasing. Around 21.4% of respondents had to take time off from work and 33.9% took medications

Table 2 Spectrum of musculoskeletal injuries amongst subgroups of endoscopic team

	Endoscopist	GI resident	Endoscopy nurse	E. technician	*P* value
Pain or numbness (%)					0.22
Yes	7 (53.8)	7 (77.8)	13 (86.7)	15 (78.9)	
No	6 (46.2)	2 (22.2)	2 (13.3)	4 (21.1)	
Left thumb pain (%)					0.02
Yes	2 (15.4)	0	2 (13.3)	0	
No	11 (84.6)	9 (100)	13 (86.7)	19 (100)	
Right thumb pain (%)					
Yes	0	3 (33.3)	0	0	
No	13 (100)	6 (66.7)	15 (100)	19 (100)	
Left shoulder pain (%)					0.48
Yes	0	0	1 (6.6)	0	
No	13 (100)	9 (100)	14 (93.4)	19 (100)	
Right shoulder pain (%)					
Yes	0	1 (11.1)	0	0	
No	13 (100)	8 (88.9)	15 (100)	19 (100)	
Both shoulder pain (%)					
Yes	2 (15.4)	2 (22.2)	3 (20)	3 (15.7)	
No	11 (84.6)	7 (77.8)	12 (80)	16 (84.)	
Left hand pain (%)					0.06
Yes	0	0	2 (13.3)	0	
No	13 (100)	9 (100)	13 (86.7)	19 (100)	
Right hand pain (%)					
Yes	0	2 (22.2)	1 (6.6)	1 (5.3)	
No	13 (100)	7 (77.8)	14 (93.4)	18 (94.7)	
Both hand pain (%)					
Yes	0	0	2 (13.3)	5 (26.3)	
No	13 (100)	9 (100)	13 (86.7)	14 (73.7)	
Neck/upper back (%)					0.004
Yes	3 (23.1)	5 (55.5)	6 (40)	9 (47.3)	
No	10 (76.9)	4 (44.5)	9 (60)	10 (52.7)	
Lower back (%)					
Yes	2 (15.4)	1 (11.1)	8 (53.3)	7 (36.8)	
No	11 (84.6)	8 (88.9)	7 (46.7)	12 (63.2)	
Left elbow pain (%)					0.57
Yes	0	0	1 (6.6)	0	
No	13 (100)	9 (100)	14 (93.4)	19 (100)	
Right elbow pain (%)					
Yes	1 (7.6)	1 (11.8)	1 (6.6)	0	
No	12 (92.4)	8 (88.2)	14 (93.4)	19 (100)	
Both elbow pain (%)					
Yes	0	0	1 (6.6)	0	

No	13 (100)	9 (100)	14 (93.4)	19 (100)	
L hand numbness (%)					0.59
Yes	1 (7.6)	0	1 (6.6)	0	
No	12 (92.4)	9 (100)	14 (93.4)	19 (100)	
R hand numbness (%)					
Yes	0	1 (11.1)	0	1 (5.2)	
No	13 (100)	8 (88.9)	15 (100)	18 (94.8)	
B/l hand numbness (%)					
Yes	0	0	1 (6.6)	0	
No	13 (100)	9 (100)	14 (93.4)	19 (100)	
Carpal tunnel (%)					0.00
Yes	0	0	2 (13.3)	2 (10.5)	
No	13 (100)	9 (100)	13 (86.6)	17 (89.5)	

GI: Gastrointestinal.

for resolution of pain.

Assessment of facilities and awareness of ergonomics

The responders were asked if they used some modifications to prevent these injuries (Supplementary Material 1). Specific modifications that were assessed were placing the endoscopic monitor at eye level (21.4%) or cardiac monitor in front (12.5%), stopping the procedure to move patients (8.9%), sitting while performing a colonoscopy (12.5%), and using height-adjustable patient beds (23.2%).

All 5 tertiary care institutions ensured that the endoscopist monitor was located directly in front of the endoscopist and monitor boom, mobile stands, and endoscope support stands were available (Figure 2). All 5 hospitals also ensured that the patient examination table was height adjustable. Four out of the 5 hospitals had a tiltable examination table. Three out of 5 tertiary setups had adjustable monitor height, adjustable cardiac monitor, 2-piece lead aprons, non-slip flooring, and covered bundled wires. Three of 5 hospitals also had an ERCP room in the endoscopy suite.

One hospital provided an adjustable computer station and none of the institutions provided anti-fatigue mats/gel floor pads or had a time-out session of 10 min or more in between two consecutive endoscopy patients.

DISCUSSION

In this study, we tried to shed light on challenges affecting MSI in endoscopists and their ancillary staff. Numerous studies have identified procedure volume and number of years in practice to be a risk factors for injury[10]. In this study, we documenting the prevalence of such injuries, the awareness and practice of ergonomic intervention by current endoscopists and the ancillary staff, as well as the availability and use of ergonomic facilities in our tertiary care institutions.

Prevalence and awareness of musculoskeletal injury

Workplace injury has undoubtedly put an additional strain on the already chronic shortage of specialists. It can harm the productivity of healthcare workers and cause long-term pain and disability.

The overall prevalence of pain or has been reported among reporting endoscopists to be as high as 29% to 89% in numerous literature[1,5,11,12]. Our study confirmed these results, with our respondents acknowledging the prevalence of such pain and injury in 75% of our subjects, similar to Hansel *et al*[5] at 74%. In the largest survey done, examining endoscopy-related MSI, which targeted members of the American Society for Gastrointestinal Endoscopy (ASGE), 53% of endoscopists had reported injuries [13]. Similarly, in a study involving 190 endoscopists in Japan, 43% reported musculoskeletal pain[14].

The site of injury plays an important role in the hindrance of an endoscopist's work. The three most commonly affected anatomical regions in our series were the neck, lower back, and shoulders, at 41.1%, 32.1%, and 21.4%, respectively. These numbers were partially contradictory to most articles we found, such as Han *et al*[15] quoting shoulders and back at approximately 42% and 38%, respectively, and Villa *et al*[3] signifying the right wrist and left thumb being the most affected at 53% and 48%, respectively.

Table 3 Spectrum of musculoskeletal injuries according to gender amongst various subgroups in the endoscopic team

	Male				*P* value	Female				*P* value
	Endoscopist (%)	GI resident (%)	Nurse (%)	Technicians (%)		Endoscopist (%)	GI resident (%)	Nurse (%)	Technicians (%)	
Pain					0.536					0.148
Yes	7 (58.3)	5 (71.4)	2 (100)	14 (77.8)		0 (0)	2 (100)	11 (84.6)	1 (100)	
No	5 (41.7)	2 (28.6)	0	4 (22.2)		1 (100)	0	2 (15.4)	0	
Thumb pain					0.028					0.207
Left	2 (16.7)	0	0	0		0	0	2 (15.4)	0	
Right	0	2 (28.6)	0	0		0	1 (50)	0	0	
No	10 (83.3)	5 (71.4)	2 (100)	18 (100)		1 (100)	1 (50)	11 (84.6)	18	
Shoulder pain					0.472					0.152
Yes	2 (16.7)	2 (28.6)	1 (50)	2 (11.1)		0	1 (50)	3 (23.1)	1 (100)	
No	10 (83.3)	5 (71.4)	1 (50)	16 (88.9)		1 (100)	1 (50)	13 (76.9)	0	
Hand					0.001					0.898
Left	0	0	1 (50)	0		0	0	1 (7.7)	0	
Right	0	1 (14.2)	0	1 (5.55)		0	1 (50)	1 (7.7)	0	
Both	0	0	0	5 (27.7)		0	0	2 (15.4)	0	
No	12 (100)	6 (85.7)	1 (50)	12 (66.6)		1 (100)	1 (50)	9 (69.2)	1 (100)	
Neck pain					0.029					0.258
Yes	3 (25)	3 (42.9)	0 (0)	8 (66)		0 (0)	2 (100)	6 (46.2)	1 (100)	
No	9 (75)	4 (57.1)	2 (100)	4 (44)		1 (100)	0 (0)	7 (53.8)	0	
Lower back pain					0.003					0.3
Yes	2 (16.7)	1 (14.3)	2 (100)	6 (54.5)		0 (0)	0 (0)	6 (46.2)	1 (100)	
No	10 (83.3)	6 (85.7)	0	5 (45.5)		1 (100)	2 (100)	7 (53.8)	0	
Elbow pain					0.468					0.99
Yes	1 (8.3)	1 (14.3)	0	0		0 (0)	0 (0)	3 (23.1)	0	
No	11 (91.7)	6 (85.7)	2 (100)	18 (100)		1 (100)	2 (100)	10 (76.9)	1	
Hand numbness					0.75					0.489
Left	1 (8.3)	0	0 (0)	1 (5.6)		0 (0)	1 (50)	2 (15.4)	0	
Right	11 (91.7)	7	2 (100)	17 (94.4)		1 (100)	1 (50)	11 (84.6)	1	
Both										
No										
Carpal tunnel					0.007					0.874
Yes	0	0	0	2 (22)		0 (0)	0	2 (15.4)	0	
No	12	7	2	7 (78)		1 (100)	2	11 (84.6)	1	

Although literature such as Villa *et al*[3] reported almost half of their subjects, 47%, acknowledging pain related to that of endoscopies, our study reflected one-third (33.3%) of our respondents attributing their symptoms due to such procedures. This could be identified as a lack of awareness or as a reluctance to practice ergonomic activities in the endoscopy suites.

Although three-quarters of our respondents acknowledging the presence of pain, surprisingly, 52.4% stated that they could not be certain whether endoscopy was a cause of their symptoms, and 14.3% said their symptoms were not caused by performing these procedures.

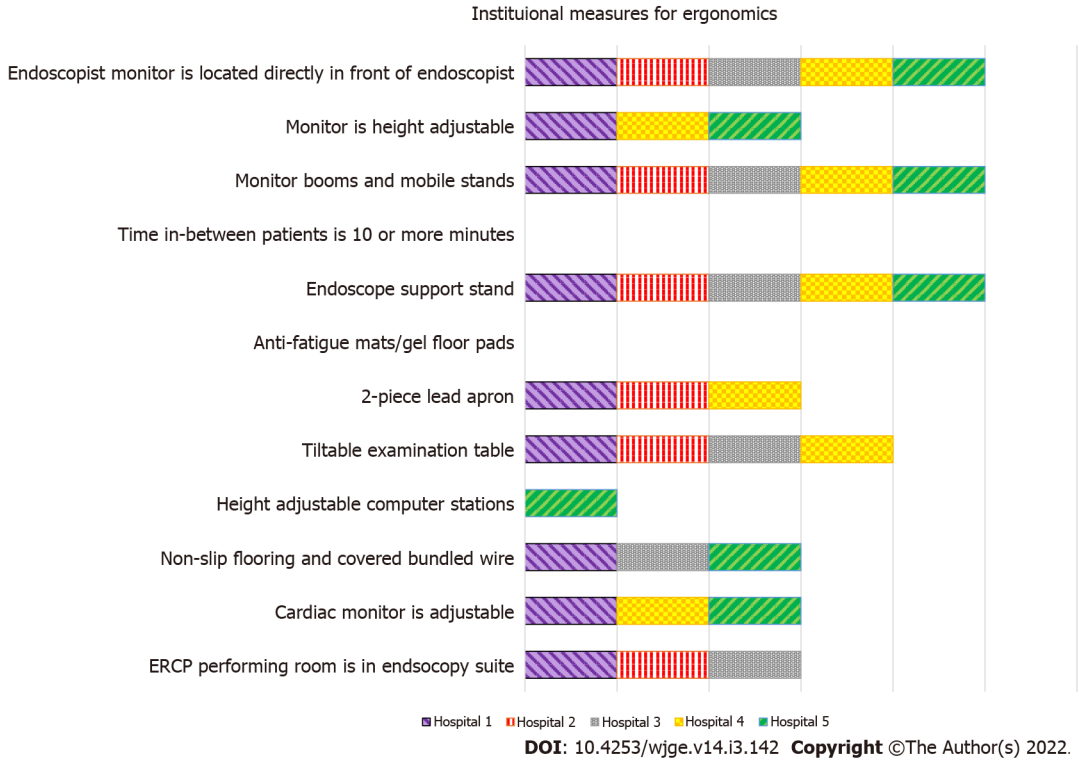

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Figure 2 An individual hospital representation of ergonomic-based facilities present. ERCP: Endoscopic retrograde cholangiopancreatography.

Some of the most important factors are repetitive movements, overuse of muscles, and prolonged standing, all of which are important parts of conducting an endoscopy. Some studies even go as far as quoting more than 16 h or 20 cases per week can lead to an increase in the risk of MSI[10,12]. Although factors leading to these injuries were not directly studied in our numbers, previous literature shed some light as stated above.

Arguably, gender does play a role according to a study conducted in ASGE fellows, which reported female gender as the only significant risk factor for MSI based on factors pertaining to their hand size and grip strength[13]. However, in our study, with only 30.3% females, a relative comparison showed no gender-related difference in MSI (Table 3).

Most literature on the prevalence of endoscopic MSI did not evaluate the impact of regular activity and work. Alarmingly, we noted 21.4% of our respondents had to take time off from work due to endoscopy-related pain. This number was an increase from other literature we found and can be subjectively linked to limited specialists and ancillary staff in this field in the city and long working hours this entails[2,5]. Morais *et al*[2] recently conducted a study amongst Portuguese endoscopists, and found that 10.1% of their respondents took time off on account of endoscopy-related injuries, with a median of 30 d. This number contrasts with previous literature in which only a few endoscopists reported missing work and only for a few days[5].

In regards to our study, this significant loss of productivity needs to be properly addressed. This will ensure avoidable time off and lead to a decreased load on fellow endoscopists and ancillary staff.

Awareness and implementation of facilities for ergonomics

Our study further investigated what measures are being taken by the endoscopists at an institutional level to decrease MSI. For example, the availability and use of portable and/or flexible endoscopy and cardiac/vital monitors can play a vital role in preventing injuries[8].

Documentation of injuries is the first step in improving and promoting discussion on workplace ergonomics as indicated in a national survey by Austin *et al*[13], where gastroenterology trainees and program directors were approached pre- and post- ergonomic training, and 90% of participants reportedly agreed that the ergonomic training sessions had a positive impact. These trainings eventually led to a decrease in the number of injuries and the creation a more ergonomic friendly work environment for endoscopists. Such practices are uncommon in our institutions.

Multiple factors were questioned in our survey that we compiled based on the current literature search and the proven adjustments and maneuvers that played a role in ergonomics[8]. Out of the total, 23.2% adjusted the height-adjustable-bed, 12.5% placed a cardiac monitor in front, 8.9% stopped to move patients, and 8.9% sat while performing the procedure. Such low numbers speak volumes on the limited awareness of ergonomics, despite the availability of these possibilities, and also shed light on why ergonomic sessions must be undertaken in the initial training months of endoscopy. Regional pain

as described above could all be caused due to poor posture. Lack of posture and ergonomic timeouts play a vital role in such context. Effective strategies to ensure good posture can significantly improve endoscopists' pain.

To avoid improper positioning, endoscopy units should consider having an "ergonomic timeout" before starting a procedure to ensure proper bed height, patient position, and monitor location[3,11]. There is a clear role for widespread education and the implementation of guidelines for the best clinical practice of ergonomics[6,7,11,16]. It is easy to see the need for more training to ensure a higher percentage of respondents take preventive measures to improve their quality of life.

Assessment of facilities at endoscopy suite

To elucidate this aspect, our 13-point checklist was studied at five tertiary care hospitals, where we examined the accessibility to basic endoscopy suite ergonomic capabilities in the devices used for every endoscopic procedure. Out of the five hospitals, none of them had a time out of ten mins or more between two patients, which could lead to patient identification errors and would give insufficient time for the endoscopist to complete individualized patient reports. A 10-min time-out would also support decreased muscle fatigue levels.

Height-adjustable examination beds, endoscopy support stand, monitor booms, and having the accessibility of the main endoscopic camera screen in front were available in all five tertiary care facilities.

None of the hospitals had any form of anti-fatigue mats or gel floor pads, however, three of them did have anti-slip flooring with wires being covered for protection against tripping over. Three of the hospitals also had movable cardiac/vital monitors alongside height-adjustable monitors for the endoscopist. One of the tertiary care hospitals had an adjustable computer station, while three of the hospitals had the ERCP procedure room within the reaches of the endoscopic procedure room.

Limitations

Our respondents were limited to 56 participants. For ergonomic evaluations, only five units in a geographic area limit the generalizability of the findings. An analysis of the pre- and post- ergonomic training with quantitative and qualitative analysis on our subjects would have added to the reliability of our findings.

CONCLUSION

This is the first study to be conducted in Pakistan for injuries caused by endoscopy. Our endoscopists had a significant prevalence of MSI leading to hindrance in their day-to-day activities and professional continuity.

Lack of knowledge and awareness of such injuries, both at a personal and institutional level, need to be addressed. Multiple areas need to be addressed in a strategic approach. We must increase awareness of these injuries among endoscopists and staff and standardized curricula to educate fellows on ergonomic practices to reduce the early development of overuse injuries. Institutions should also have standardized ergonomic protocols in place in endoscopy suites.

More research is needed to document the efficacy of an intervention in improving quality of life and productivity.

ARTICLE HIGHLIGHTS

Research background

Ergonomics in the field of gastroenterology with regards to musculoskeletal injuries (MSI) among endoscopists and ancillary staff have been highlighted in studies from the western world. MSI affect the quality and longevity of the gastroenterologist, which can lead to a shortage of specialists. There has been a dearth of literature on the topic from our region.

Research motivation

The goal of this research was to create awareness about the importance of ergonomics in endoscopy that may prevent future injuries. Research would lead towards the modification and development of more ergonomic endoscopes and techniques. Furthermore, procedure rooms and spaces with institutional emphasis would promote strategies for the management of musculoskeletal injury.

Research objectives

Our objective is to document the prevalence of MSI, awareness, and practice of ergonomics by endoscopists, ancillary staff, and institutions.

Research methods

An observational cross-sectional study in Karachi. An eleven-point self-administered questionnaire was distributed and used to evaluate MSI and ergonomic adjustments amongst three tertiary care setups in Karachi. An onsite survey *via* a 13-point checklist for endoscopy suite facilities was used to assess the ergonomically friendly conveniences at five tertiary care setups.

Research results

There were 56 participants in total with 39 (69.6%) males. Pain and numbness were documented by 75% of the respondents, with the neck (41.1%) and lower back (32.1%) being the most commonly affected regions. Twenty one point four percent had to take time off their work, while 33.9% took medications for pain. Ergonomic modifications to prevent musculoskeletal injury were used by 21.4%. Institutions lacked sufficient ergonomic facilities.

Research conclusions

Three-fourth of our endoscopists reported MSI, of which more than half are not sure or attributed this problem to endoscopy. The prevalence of MSI warrants urgent attention.

Research perspectives

It would be interesting to see interventions to improve the ergonomics among participants, such as pre- and post-intervention improvement and the impact of creating awareness. Research can be directed towards the development of curriculum and guidelines addressing ergonomics and modifications to prevent MSI.

ACKNOWLEDGEMENTS

We thank all the respondents for taking out their time to fill in our questionnaire and also thank the following five hospitals for allowing us to examine their endoscopy suites: Aga Khan University Hospital, Liaquat National Hospital, Ziauddin University Hospital, Dr. Ruth K. M. Pfau Civil Hospital and Sindh Institute of Urology and Transplant.

FOOTNOTES

Author contributions: Shah SZ designed the study and methodology for the study and contributed to the finalized article writing; Abid S conceptualized the idea, edited and revised the manuscript and oversaw the entire project; Rehman ST and Hussain MM contributed to initial and finalized article writing and analysis alongside literature search; Ali M, Khan A and Sarwar S contributed in data collection and analysis.

Institutional review board statement: The study was reviewed and approved by the Ethics Review Committees (ERC) at the Aga Khan University (Karachi, Pakistan).

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

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ORIGINAL ARTICLE

Observational Study

SARS-CoV-2 in inflammatory bowel disease population: Antibodies, disease and correlation with therapy

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Abstract

BACKGROUND

Guidelines recommend to cease inflammatory bowel disease (IBD) biologic therapy during coronavirus disease 2019 (COVID-19).

AIM

To investigate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody positivity in an IBD cohort, COVID-19 disease severity and to evaluate the correlation with clinical/therapeutic variables.

METHODS

Prospective observational cohort study. IBD patients were tested for SARS-CoV-2 IgG. Data on COVID-19 disease, demographics/therapeutics and clinical features of the IBD population were collected. IgG ≥ 7 was set for SARS-CoV-2 antibody positivity. Throat swab was performed in cases of IgG positivity. Correlations between antibody positivity or COVID-19 symptoms and therapeutic/clinical data were assessed.

RESULTS

In total, 103 IBD patients were enrolled. Among them, 18.4% had IgG ≥ 7. Multivariate analysis of antibody positivity correlated only with IBD treatment. For IgG ≥ 7, the odds ratio was 1.44 and 0.16 for azathioprine and mesalazine, respectively, *vs* biologic drugs (P = 0.0157 between them). COVID-19 related symptoms were reported in 63% of patients with IgG positivity. All but one

patient with COVID-19 symptoms did not require ceasing IBD treatment or hospitalization. IBD treatment and body mass index correlated with COVID-19 disease development with symptoms.

CONCLUSION

The IBD population does not have a higher risk of severe COVID-19. The relative risk of having SARS-CoV-2 antibodies and symptoms was higher for patients taking azathioprine, then biologic therapy and lastly mesalazine. None of the patients under biologic therapy developed severe COVID-19.

Key Words: Inflammatory bowel disease; SARS-CoV-2; COVID-19; Biologic treatment; SARS-CoV-2 antibody; Inflammatory bowel disease therapy

Core Tip: Guidelines recommend ceasing inflammatory bowel disease (IBD) biologic therapy during coronavirus disease 2019 (COVID-19). IBD patients were prospectively tested for severe acute respiratory syndrome coronavirus 2 IgG. In total, 103 IBD patients were enrolled. We found that 18.4% had IgG positivity, and 63% developed COVID-19 disease with symptoms. However, all but one patient with symptoms did not require ceasing IBD treatment no hospitalization. None of the patients under biologic therapy developed severe COVID-19. Therefore, the IBD population does not seem to have a high risk of severe COVID-19, particularly if under biological treatment or mesalazine.

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INTRODUCTION

A new β-coronavirus (SARS-CoV-2) spread in November 2019 in China and then worldwide, becoming a pandemic. The related disease, known as coronavirus disease 2019 (COVID-19), mainly involves the respiratory system. The elderly and patients affected by chronic diseases seem to be at a higher risk to develop severe pneumonia and acute distress syndrome[1]. In this scenario, the patients affected by inflammatory bowel diseases (IBD) appeared to be an at-risk population for severe COVID-19, considering the possible gastrointestinal system involvement[2-6]. Indeed, it seems that the high expression of angiotensin-converting enzyme 2 in the intestinal tract, above all in the absorptive enterocytes of the ileum and colon and in the epithelial cells of the esophagus, makes these tissues highly susceptible to SARS-CoV-2 infection. Mucosal damage was observed in the esophagus, stomach, duodenum and rectum by histological examinations as plasma cells and lymphocytes infiltrated the lamina propria. Approximately 3% of COVID-19 cases have only digestive symptoms. Moreover, the detection of SARS-CoV-2 in the stool suggested that the virus could replicate in the digestive tract[6].

Initial indications from an IBD center in Wuhan, China was to discontinue all biological and immunosuppressive treatments. They reported that among 318 registered IBD patients, none developed COVID-19[7]. Nevertheless, scientific societies suggested that IBD patients should continue the ongoing treatment to avoid relapse, including the biological therapies[1]. However, regarding IBD patients affected by COVID-19, guidelines suggest handling the treatments with more caution. In particular, the American Gastroenterological Association guidelines divided them into three different categories: IBD patients without SARS-CoV-2 infection; IBD patients with SARS-CoV-2 infection but no symptoms of COVID-19; and IBD patients with COVID-19 symptoms. The first category should continue all treatments. The second category should discontinue thiopurines, methotrexate and tofacitinib and delay biological therapies for 2 wk while monitoring symptoms of COVID-19. The third category should discontinue thiopurines, methotrexate, tofacitinib and biological therapy during the illness[1].

Since the scientific community had to develop new guidelines in a short time with a new and unknown disease, the recommendations carry a low grade of evidence. In an Italian cohort of 522 IBD patients, none were hospitalized for SARS-CoV-2 infection, and 16% of the patients were under biologic treatment. However, 11% of the patients were children, a population with an unclear susceptibility to the virus[8]. Moreover, some interesting observational studies report COVID-19 prevalence and symptoms/outcomes in IBD cohorts[9,10]. However, little is known about the possible role of IBD treatments in the development of severe COVID-19 disease. Importantly, it remains unclear whether

IBD patients are at a higher or lower risk of severe COVID-19.

Systemic inflammation is a crucial target for the treatment of COVID-19 pneumonia, as the severity of the respiratory disease seems to be linked to the upregulation of inflammatory cytokines by creating a "cytokine storm," producing interleukin (IL)-6, IL-1, tumor necrosis factor (TNF) and interferon-γ. The exaggerated synthesis of IL-6 can lead to an acute severe systemic inflammatory response. It should be noted that cytokine blockers and Jak inhibitors were considered for clinical therapy of COVID-19 acute respiratory distress syndrome[11-13]. Interestingly, TNF inhibition has also been suggested in selected patients with high IL-6 levels. Indeed, when TNF is blocked, there is a serial decrease of IL-6 and IL-1 within 12 h in patients with active rheumatoid arthritis. A reduction of adhesion molecules and vascular endothelial growth factor was observed as well[14]. Nevertheless, no definitive treatment has been approved. Therefore, many hypotheses but few certainties are present. In particular, COVID-19 outcomes in patients with IBD immunomodulant/immunosuppressive treatments remains under debate.

The present study aimed to investigate the prevalence of SARS-CoV-2 antibody positivity and COVID-19 disease severity in an IBD cohort, in both symptomatic and asymptomatic patients and to evaluate the correlation with clinical/therapeutic variables.

MATERIALS AND METHODS

Study design

We conducted a prospective cohort study. The informed consent for the study was obtained from all the patients in accordance with the World Medical Association's 2008 Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. The privacy rights of patients were always observed. All authors had access to the study data and reviewed and approved the final manuscript.

Patients

Cohort of patients affected by IBD (Crohn's disease or ulcerative colitis). From April 22, 2020 to May 31, 2020, each IBD patient followed-up at ASST Cremona was offered to participate in the study. The patients were consecutively enrolled.

Data collection

Each IBD patient was asked about his/her recent clinical history (respiratory and gastrointestinal symptoms) from the beginning of the COVID-19 pandemic in Europe (February 21, 2020) by completing a questionnaire, and all the information was validated with the doctor who conducted the interview. Data collected in the questionnaire were summarized in the Supplementary Material.

Age, sex, body mass index (BMI), IBD type, treatments and clinical activity and other comorbidities were anonymously collected in a database. Charlson Comorbidity Index was calculated for each patient.

Antibody testing

A single blood test was performed for each patient to search for anti-SARS-CoV-2 IgG. The LIAISON® SARS-CoV-2 S1/S2 IgG test [Diasorin S.p.A, Saluggia (VC) – Italy] was used according to manufacturer's instructions. S1 and S2 are subunits of the spike protein and are responsible for binding (S1) and fusion (S2) of the virus to cells. The spike protein is the target of neutralizing antibodies. They are defined as antibodies that protect cells from pathogens or infectious particles by neutralizing their biological effects. The manufacturer reports a positive agreement of 94.4% [95% confidence interval (CI): 88.8%-97.2%] with the plaque reduction neutralization test. The IgG test has diagnostic specificity of 98.5% (95%CI: 97.5%-99.2%) in blood donors and 98.9% in presumably SARS-Cov-2 negative diagnostic routine samples. The IgG values are considered negative when < 12.0 kAU/L, equivocal from 12 kAU/L to 15.0 kAU/L and positive when ≥ 15.0 kAU/L. When applying a cutoff of >15 kAU/L, the reported test's sensitivity is time-dependent: 25% (14.6%-39.4%) ≤ 5 d after reverse transcriptase-PCR-confirmed diagnosis; 90.4% (79.4%-95.8%) from day 5 to day 15; and 97.4% (86.8%-99.5%) after > 15 d from PCR diagnosis[15]. However, Plebani *et al*[16] found that 6.2 kAU/L was the appropriate cutoff for the DiaSorin method to reach a sensitivity of 97.1% and a specificity of 88.9%. Moreover, in our hospital, all health care workers (HCW) were tested for serology immediately after the first 2 mo of pandemic (between April and May 2020). Among the HCW who were previously confirmed ill, only the 85% of them resulted having IgG value > 15, whereas 14% of them had values between 7 and 15 (data from National Institute of Heath, 2020).

Thus, in the present study we decided to perform the analysis using both 15 and 7 as cutoffs, considering 7 as the most reliable value.

Swab throat test

All patients who resulted positive for SARS-CoV-2 IgG were tested with a SARS-CoV-2 swab throat test during the same week using the Allplex 2019-nCoV assay (Arrow Diagnostics S.r.l., Genova, Italy),

which is a single-tube assay able to detect the three target genes (*E* gene, *RdRP* gene and *N* gene) as recommended by the World Health Organization.

Statistical analysis

Categorical variables were described as count and percentage and compared between groups with the χ^2 test. Continuous variables were described as mean and standard deviation or median and interquartile range if not normally distributed (Shapiro-Wilks test) and compared with independent *t*-test or Mann-Whitney.

Univariate and multivariate logistic regression models were used to assess: (1) Association between age, sex, BMI, IBD type, IBD treatments, IBD clinical activity, Charlson Comorbidity Index and SARS-CoV-2 IgG positivity; and (2) Association between age, sex, BMI, IBD type, IBD treatments, IBD clinical activity, Charlson Comorbidity Index and presence of COVID-19 symptoms.

The analysis was performed using SARS-CoV-2 IgG value cutoff of > 7 kAU/L (15-16).

RESULTS

In total, 103 IBD patients were consecutively enrolled; 54 had Crohn's disease and 49 ulcerative colitis. Among these, 36 patients (35.0%) were treated with biologic treatment, 14 (13.6%) with azathioprine (AZA) and 53 (51.4%) with mesalazine. Demographic, clinical and therapeutic characteristics of the cohort were summarized in Table 1**.** The survey's results were summarized in Table 2.

Prevalence of SARS-CoV-2 IgG positivity in IBD cohort

SARS-CoV-2 IgG positivity with value > 7 was found in 19 out of 103 patients (18.4%). Among them: 10 were under biological treatment; 5 under AZA; and 4 under mesalazine. Symptoms related to COVID-19 disease were reported in 12 out of 19 patients (63%). Among them, 2 were treated with mesalazine, 4 with AZA and 6 with biologic treatment. Among the 7 out of 19 patients without a history of COVID-19-related symptoms but positive for antibodies, 2 were treated with mesalazine, 1 with AZA and 4 with biologic therapy. All but one patient, who had pneumonia and was under AZA treatment, did not require hospitalization. Data regarding the patients with IgG > 7 were summarized in Table 3.

Swab throat test

All the patients with IgG > 7 were tested with a swab throat test. All of them were negative. The patient with a history of COVID-19 pneumonia had tested positive before the enrollment and tested negative after enrollment.

Correlation between SARS-CoV-2 IgG positivity and clinical/therapeutic variables in the IBD cohort

SARS-CoV-2 IgG value ≥ 7 correlated at multivariate analysis only with IBD treatment. In detail, stratifying the population for treatment, the relative risk of having SARS-COV-2 IgG ≥ 7 was higher for patients treated with AZA and lower with mesalazine. The odds ratios for AZA was 1.44 (95%CI: 0.27-7.56) and 0.16 (95%CI: 0.03-0.71) for mesalazine *vs* biologic drug (P = 0.0157 between them). The relative risk for patients under mesalazine was lower than for those under biologic therapy (P = 0.016).

Correlation between the presence of COVID-19-related symptoms and clinical/therapeutic variables in IBD cohort

The presence of COVID-19-related symptoms were correlated after multivariate analysis with BMI (P = 0.05) and with IBD therapy. The relative risk of having symptoms was higher for patients treated with AZA and lower with mesalazine *vs* biologic drug: odds ratios 7.47 (95%CI: 1.22-45.73) and 0.52 (95%CI: 0.17-1.72, P = 0.03) for AZA and mesalazine, respectively (P = 0.004 between them).

DISCUSSION

The use of SARS-Cov-2 antibodies to monitor the immunity against COVID-19 remains a matter of debate in the general population. However, the presence of SARS-CoV-2 IgG antibodies certify the previous or recent infection[17]. In our hospital, all health care workers (HCW) were tested for serology immediately after the first 2 mo of pandemic, in the same week of the start of our study on IBD cohort. 364 out of 1600 operators were diagnosed as affected by COVID-19 between February 21 and April 22 and all of them tested positive for SARS-CoV-2 swab throat test. Among the HCWs who were previously confirmed ill, the 99% resulted having IgG3 value > 7. Interestingly, 20% of operators who did not report symptoms suggestive for COVID-19 resulted having SARS-CoV-2 antibodies ≥ 7. (data from National Institute of Health, 2020). This observation confirms the presence of an unknown number of asymptomatic infected people[18]. The available studies on the serum concentration of IgG after

Table 1 Demographic, clinical and therapeutic characteristics of the inflammatory bowel disease cohort

Therapy	Characteristics (*n*, %)	Disease		Total (*n*)
		CD (*n*)	UC (*n*)	
Biologic treatment	Male (15, 41.6)	13	3	36
	Woman (20, 55.5)	15	5	
	BMI > 30 (5, 13.8)	3	2	
	BMI < 30 (31, 82.2)	25	6	
	Comorbidities yes (14, 38.8)	11	3	
	Comorbidities no (22, 61.2)	17	5	
	Age > 65 (5, 13.8)	2	3	
	Age < 65 (31, 86.2)	26	5	
Azathioprine	Male (9, 64.2)	3	6	14
	Woman (5, 35.7)	2	3	
	BMI > 30 (1, 7.1)	1	0	
	BMI < 30 (13, 92.8)	4	9	
	Comorbidities yes (6, 42.8)	2	4	
	Comorbidities no (8, 57.1)	3	5	
	Age > 65 (3, 21.4)	1	2	
	Age < 65 (11, 78.6)	4	7	
Mesalazine	Male (23, 43.4)	10	13	53
	Woman (30, 56.6)	11	19	
	BMI > 30 (6, 11.3)	2	4	
	BMI < 30 (47, 88.7)	19	28	
	Comorbidities yes (30, 56.6)	10	20	
	Comorbidities no (23, 43.3)	11	12	
	Age > 65 (19, 35.8)	10	9	
	Age < 65 (34, 64.2)	11	23	
		54	49	103

BMI: Body mass index; CD: Crohn's disease; UC: Ulcerative colitis.

COVID-19 infection revealed conflicting results and the duration of antibodies rises is currently unknown, but is estimated around 9 mo (data from National Institute of Health, 2021). There is a possible decrease of IgG title after the first two wk of infection and it is unclear whether the test is able to detect lower antibody levels in milder and asymptomatic COVID-19 disease[17-20]. Plebani group tried to harmonize the thresholds to allow a larger agreement on IgG anti Sars-Cov-2 antibodies determination. They found 6.2 KAU/L as the cut off for Diasorin method to reach a sensitivity of 97.1% and a specificity of 88.9% for the diagnosis of SARS-CoV-2 infection[16]. Our data are thus in line with this latter observation. The COVID-19 symptoms occurred in IBD patients at least 1 mo before the interview. During the time between the symptoms and the enrollment, they lived the complete lock down, established in Italy from March 9 to May 18. They tested all negative at the swab test performed at the enrollment. This is in line with the overall sensitivity of the test, ranging from 56 to 83%: 66.7% in the first week of the infection and lower in the following wk observation that the SARS-CoV-2 positivity in the swab[21].

Prevalence of patients with SARS-CoV-2 IgG positivity in our cohort was 18.4%. This means that those patients got infected with SARS-CoV-2 virus in the previous period, but only 63% of them developed the disease, reporting symptoms. Moreover, only one patient required hospitalization for pneumonia. The patients with history of COVID-19 related symptoms mainly had mild respiratory symptoms or minor manifestations. None but one patient (5%) required hospitalization, but without the need of intensive care unit. Conversely, in the general population, during both the first and the second

Table 2 Survey responses of 103 inflammatory bowel disease patients

Survey answers					
Close contacts with positive patients (*n*, %)		Yes	17, 16.5		
		No	85, 82.5		
		Nd	1, 1		
Tested for swab (*n*, %)		Yes	13, 12.5	Positive	1, 1
				Negative	12, 11.5
		No	90, 87.5		
Symptoms (*n*, %)	No symptoms		49, 47.5		
	Mild	Cough	19, 18.4		
		Changes in taste/smell	6, 5.8		
		Muscle and joint pain	12, 11.6		
		Asthenia	11, 10.6		
		Fever	18, 17.4		
		GI symptoms	23, 22.3		
	Severe	Mild dyspnea	4, 3.8		
		Pneumonia	1, 0.9		
Total number of patients (*n*)					103

GI: Gastrointestinal; Nd: Not determined.

Table 3 Severe acute respiratory syndrome coronavirus 2 IgG positive inflammatory bowel disease patients divided by presence or absence of COVID-19 symptoms and ongoing therapy

SARS-CoV-2 IgG value > 7				
SARS-CoV-2 IgG positive patients (*n*, %)	**Therapy (patients, *n*, %)**	**Disease**		**Total *n* (%)**
		CD (*n*)	**UC (*n*)**	
COVID-19 symptoms yes (12, 63.2)	Biologic drug (6, 50.0)	5	1	6
	Azathioprine (4, 33.3)	1	3	4
	Mesalazine (2, 16.6)	0	2	2
COVID-19 symptoms no (7, 36.8)	Biologic treatment (4, 57.1)	4	0	4
	Azathioprine (1, 14.3)	0	1	1
	Mesalazine (2, 28.6)	0	2	2
		12	7	19

CD: Crohn' s disease; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; UC: Ulcerative colitis.

wave of the pandemic, 10% of people required hospitalization in intensive care unit (data from the National Institute of Health, 2021). Half of the IBD patients that resulted positive to antibody test remained asymptomatic and in 48% of cases they developed only mild symptoms. We can thus conclude that the IBD population does not seem at higher risk to develop severe COVID-19 disease in comparison with the general population, confirming the observation of Bezzio *et al*[9]. Only the patient with pneumonia hold the IBD treatment. This happened because, due to the mildness of the disease, the patients informed the general practitioner but not the IBD center about the symptoms. These data, even if do not confirm the American Gastroenterological Association guidelines strategy, gave us the opportunity to evaluate the cohort[1]. The results obtained are encouraging, as it seems that IBD patients with COVID-19 ongoing disease with symptoms could continue any treatments both avoiding IBD relapse and without a significant higher risk of developing severe COVID-19 requiring hospitalization. Differently from Bezzio *et al*[9], nobody died in our cohort; moreover, nor age neither active IBD

were significantly associated with a COVID-19 worse prognosis.

SARS-coV-2 serology resulted associated only with the ongoing IBD treatment. Among the patients having a positive serology there was a prevalence of biologic therapy. The presence of COVID-19 disease was associated with both IBD therapy and BMI. The patients who reported previous symptoms were treated with mesalazine in 2 cases, with AZA in 4 and with biological treatment in 6; the only patient with pneumonia was treated with AZA. The calculated relative risk of being infected was higher for patients treated with AZA, then for patients treated with biologic drugs and the lowest risk was found for patients treated with mesalazine. We decided to separate the different treatments in the analysis, as the AZA and the biologic therapy have a different mechanism of action: AZA is an immunosuppressive agent, whereas the biologic therapies are known as immunomodulating agents. None of the patients treated with biologic therapy developed a severe COVID-19 disease. Our results show that the use of biologic therapy does not seem to expose the patients to higher risk of severe COVID-19 disease, even when the infection is present. We did not perform a sub-analysis of the different type of biologic treatment for the small sample size. However, we report that the 80% of patients was treated with anti-TNF agents. More studies are needed to confirm whether it is appropriate to continue biological drugs for IBD patients who are affected with Sars-cov-2. The other variable associated with the presence of COVID-19 related symptoms was the BMI. This data is supported by the literature, as obesity is a factor associated with bad prognosis in the patients with COVID-19 pneumonia [22]. Interestingly, nor the old age neither the comorbidities or the type of IBD were associated with the antibody positivity or the development of COVID-19 symptoms in our study. This could be explained by the fact that these variables were associated in literature to death or very bad outcome, and none of our patients reported such complication[23].

All the 103 patients of the study had been clinically followed up for 10 mo after the beginning of the study. None of them hold the IBD treatments or developed new symptoms of COVID-19 until April 2021. After this period of time all our IBD patients had been received the vaccine against COVID-19.

The main limitation of the study is the small sample. Therefore, further studies with larger populations are needed to confirm our observations.

CONCLUSION

We investigated both the SARS-CoV-2 IgG positivity in symptomatic and asymptomatic IBD patients and the relationship between IBD therapy and COVID-19 disease severity. The results are interesting and seem encouraging for the patients treated with biologic therapy, since they don't seem to carry a high risk of developing severe COVID-19. However, further and larger studies are needed to confirm these observations.

ARTICLE HIGHLIGHTS

Research background

Guidelines recommend to hold inflammatory bowel diseases (IBD) biologic therapy during coronavirus disease 2019 (COVID-19). It is still not clear if the IBD patients carry a high risk of developing severe COVID-19.

Research motivation

IBD patients could carry a high risk of relapse or worsening of the intestinal disease in holding the therapy.

Research objectives

To investigate the prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies positivity and COVID-19 disease severity in IBD patients. Evaluate the correlation with clinical/therapeutic variables.

Research methods

Prospective cohort study. Patients with IBD were consecutively enrolled from April 22nd to May 31st 2020. Age, sex, BMI, IBD type, treatments and clinical activity and other comorbidities were anonymously collected in a Database. Charlson Comorbidity Index was calculated for each patient. A single blood test was performed to each patient to search for Immunoglobulin IgG anti SARS-Cov-2. The LIAISON® SARS-CoV-2 S1/S2 IgG test [DiasorinS.p.A, Saluggia (VC) – Italy] was used according to manufacturers' instructions. The analysis was performed using SARS-CoV-2 IgG value cut off of > 7 kAU/L. All patients who resulted positive to SARS-CoV-2 IgG were tested with SARS-CoV-2 swab throat test during the same week, using the Allplex 2019-nCoV assay (Arrow Diagnostics S.r.l., Genova,

Italy) a single-tube assay able to detect the three target genes (E gene, RdRP gene and N gene) as in the WHO recommended protocols. Categorical variables were described as count and percentage and compared between groups with chi square test; continuous variables were described as mean and standard deviation or median and inter-quartile range if not normally distributed (Shapiro-Wilks test) and compared with independent t- test or Mann-Whitney. Through univariate and multivariate logistic regression models were assessed: association between age, sex, BMI, IBD type, IBD treatments, IBD clinical activity, Charlson Comorbidity Index and SARS-CoV-2 IgG positivity or the presence of COVID-19 symptoms.

Research results

103 IBD consecutive patients were enrolled: 54 with Crohn's disease and 49 ulcerative colitis. 36 patients (35%) were treated with biologic treatment, 14 (13.6%) with azathioprine (AZA) and 53 (51.4%) with mesalazine. 19 out of 103 patients (18.4%) had SARS-CoV-2 IgG positivity, with value > 7. Among them: 10 were under biological treatment, 5 under AZA and 4 under mesalazine. 12 out of 19 (63%) reported symptoms related to COVID-19 disease. Among them, 2 were treated with mesalazine, 4 with AZA and 6 with biologic treatment. Among the 7 out 19 patients without history of COVID-19 related symptoms, but positive for antibodies, 2 were treated with mesalazine, one with AZA and 4 with biologic therapy. All but one patient, who had pneumonia and was under AZA treatment, did not require hospitalization. All the patients with IgG > 7 were tested for swab throat test. All of them resulted negative at the enrollment. SARS-CoV-2 IgG value ≥ 7 correlated at multivariate analysis only with IBD treatment. The relative risk of having SARS-COV-2 IgG ≥ 7 was higher for patients treated with AZA and lower with mesalazine: odds ratio (OR) 1.44 (95%CI: 0.27-7.56) and 0.16 (95%CI: 0.03-0.71), for AZA and mesalazine, respectively, *vs* biologic drug (P = 0.0157 between them). The relative risk for patients under mesalazine was lower than for those under biologic therapy, P = 0.016. The presence of COVID-19 related symptoms resulted correlated at multivariate analysis with Body Mass Index (BMI), P = 0.05 and with IBD therapy. The relative risk of having symptoms was strongly higher for patients treated with AZA and lower with mesalazine *vs* biologic drug: odds ratio (OR) 7.47 (95%CI: 1.22-45.73) and 0.52 (95%CI: 0.17-1.72, P = 0.03), for AZA and mesalazine, respectively (P = 0.004 between them).

Research conclusions

The patients treated with biologic therapy don't seem to carry a high risk of developing severe COVID-19.

Research perspectives

The patients treated with biologic therapy don't seem to carry a high risk of developing severe COVID-19. Therefore, further and larger studies are needed to confirm these observations and to understand if the strategy to hold the IBD treatment during COVID-19 disease could be modified.

FOOTNOTES

Author contributions: Conti CB and Grassia R conceived and planned the study; Mainardi E, Grassia R, Drago A, Cereatti F, Soro S and Testa S carried out the tests and collected the data; Testa S and Mainardi E contributed to the interpretation of the results; De Silvestri A performed the statistical analysis; Conti CB wrote the manuscript; all authors provided critical feedback and helped the research and analysis of the manuscript.

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SYSTEMATIC REVIEWS

Endoscopic management and outcome of non-variceal bleeding in patients with liver cirrhosis: A systematic review

Georgios Demetriou, Aikaterini Augoustaki, Evangelos Kalaitzakis

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Abstract

BACKGROUND

Acute non-variceal bleeding accounts for approximately 20% of all-cause bleeding episodes in patients with liver cirrhosis. It is associated with high morbidity and mortality therefore prompt diagnosis and endoscopic management are crucial.

AIM

To evaluate available data on the efficacy of endoscopic treatment modalities used to control acute non-variceal gastrointestinal bleeding (GIB) in cirrhotic patients as well as to assess treatment outcomes.

METHODS

Employing PRISMA methodology, the MEDLINE was searched through PubMed using appropriate MeSH terms. Data are reported in a summative manner and separately for each major non-variceal cause of bleeding.

RESULTS

Overall, 23 studies were identified with a total of 1288 cirrhotic patients of whom 958/1288 underwent endoscopic therapy for acute non-variceal GIB. Peptic ulcer bleeding was the most common cause of acute non-variceal bleeding, followed by portal hypertensive gastropathy, gastric antral vascular ectasia, Mallory-Weiss syndrome, Dieaulafoy lesions, portal hypertensive colopathy, and hemorrhoids. Failure to control bleeding from all-causes of non-variceal GIB accounted for less than 3.5% of cirrhotic patients. Rebleeding (range 2%-25%) and mortality (range 3%-40%) rates varied, presumably due to study heterogeneity. Rebleeding was usually managed endoscopically and salvage therapy using arterial embolisation or surgery was undertaken in very few cases. Mortality was usually associated with liver function deterioration and other organ failure or infections rather than uncontrolled bleeding. Endoscopic treatment-related complications were extremely rare. Lower acute non-variceal bleeding was examined in two studies (197/1288 patients) achieving initial hemostasis in all patients using argon plasma coagulation for portal hypertensive colopathy and endoscopic band ligation or

sclerotherapy for bleeding hemorrhoids (rebleeding range 10%-13%). Data on the efficacy of endoscopic therapy of cirrhotic patients *vs* non-cirrhotic controls with acute GIB are very scarce.

CONCLUSION

Endotherapy seems to be efficient as a means to control non-variceal hemorrhage in cirrhosis, although published data are very limited, particularly those comparing cirrhotics with non-cirrhotics and those regarding acute bleeding from the lower gastrointestinal tract. Rebleeding and mortality rates appear to be relatively high, although firm conclusions may not be drawn due to study heterogeneity. Hopefully this review may stimulate further research on this subject and help clinicians administer optimal endoscopic therapy for cirrhotic patients.

Key Words: Liver cirrhosis; Non-variceal gastrointestinal hemorrhage; Gastrointestinal endoscopy; Endoscopic therapy; Patient outcomes; Peptic ulcer; Mallory Weiss syndrome; Gastric antral vascular ectasia

Core Tip: Acute non-variceal gastrointestinal bleeding (ANVGIB) is not uncommon in cirrhotic patients. Survival of these patients has improved in recent years due to the evolution of both endoscopic and pharmacologic treatment. However data on most sources of ANVGIB and the efficacy of endoscopic therapy in cirrhosis are very limited, while similar data on acute bleeding from the lower gastrointestinal tract are almost non-existent in this group of patients. We herein present endoscopic modalities used to control ANVGIB and post-treatment outcomes in patients with liver cirrhosis. Our review highlights that endoscopic therapy seems to be effective in these patients, although comparative data with non-cirrhotic patients are very few.

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INTRODUCTION

Acute upper gastrointestinal bleeding (AUGIB) in patients with cirrhosis is a detrimental complication resulting in high morbidity and mortality[1-3]. The source of AUGIB is most commonly related to portal hypertension and occurs mainly from gastroesophageal varices (60%-75%). However, a non-negligible number (20%-30%) of cirrhotic patients present with non-variceal gastrointestinal bleeding (NVGIB) with peptic ulcer being the leading cause[2,4-7]. Other sources of NVGIB in this group of patients are gastric antral vascular ectasia (GAVE), portal hypertensive gastropathy (PHG), portal hypertensive colopathy (PHC), Dieulafoy's lesions (DL), Mallory-Weiss syndrome (MWS), and hemorrhoids[8].

Regardless of the bleeding source, treatment and endoscopic control of haemorrhage can be really challenging due to the fragility of these patients and coagulopathy disorders in cirrhosis[9,10]. Albeit mortality rates have been declining in recent years due to advances in pharmaceutical and endoscopic management, the death burden remains high ranging from 15%-25% following an episode of AUGIB[3,11-14]. Although variceal bleeding in cirrhosis has been well studied, published data on outcomes of acute non-variceal upper and lower GIB are limited, with only few studies reporting the endoscopic modalities and efficacy of endoscopic therapy in patients with cirrhosis and acute NVGIB.

The aim of this systematic review was to evaluate available data on the efficacy of endoscopic treatment modalities used to control acute NVGIB in cirrhotic patients as well as to assess the treatment outcomes.

MATERIALS AND METHODS

A systematic review was conducted according to the PRISMA statement for reporting systematic reviews and meta-analyses[15]. The MEDLINE was searched through PubMed by two authors (Demetriou G, Augoustaki A) independently for relevant studies (start date: 01/01/1980, end date: 01/01/2021) using the following query: "Liver Cirrhosis" AND "Gastrointestinal Hemorrhage/therapy". All studies were eligible for inclusion except: (1) Studies in languages other than English; (2) Animal studies; (3) Cohort studies focused only on variceal bleeding; (4) Case reports (< 3 patients) or

reviews, meta-analyses, and letters; (5) Pediatric studies; (6) Iatrogenic induced haemorrhage; and (7) Studies conducted before 1980.

Our search strategy revealed 2002 relevant studies that were screened by Demetriou G and Augoustaki A according to their titles and abstracts. Following application of the exclusion criteria, 51 studies were chosen for full-text screening (Figure 1). Any disagreement was resolved by means of consensus with a third author (Kalaitzakis E). These studies were further subjected for eligibility and were excluded if: (1) Series with < 3 patients; (2) No numerical data for cirrhotic patients; (3) Not overt bleeding (overt bleeding was defined as the presence of melena and/or hematemesis and/or hematochezia or active bleeding on endoscopy); (4) No endoscopic treatment; and (5) Not at least one treatment outcome.

The list of references of all included studies and relevant review articles were checked and additional studies were included according to the eligibility criteria. A total of 23 studies were finally included for this review (Figure 1).

RESULTS

Study characteristics

The majority of the included studies (Table 1) were retrospective (15/23, 65%) while 8 (35%) were prospective. Except for two multi-center studies (9%) the remaining were single-centre (21/23, 91%). Most studies evaluated outcomes of AUGIB from a single source of bleeding, *i.e.* 7 studies from GAVE, four from peptic ulcer, four from MWS, two from PHC, two from Dieulafoy's lesion and one each from PHG and hemorrhoids. Three studies evaluated more than one sources of AUGIB.

Endoscopic treatment modalities applied to control bleeding (either as single or combination treatment) were epinephrine injection (10 studies), argon plasma coagulation (APC) (9 studies), electrocoagulation (6 studies), hemocliping (5 studies), injection sclerotherapy (polidocanol, N-butyl-cyanoacrylate, histoacryl) (5 studies), endoscopic band ligation (EBL) (4 studies), heater probe coagulation (3 studies), laser coagulation (1 study), and hemospray (1 study). The most common outcomes in the majority of the studies were success in control of bleeding, rebleeding, and mortality.

Overall, 1288 cirrhotic patients were included in the 23 studies identified by means of our search and 958/1288 underwent endoscopic therapy for non-variceal acute gastrointestinal bleeding (NVAGIB) (Tables 1-4). Failure to control bleeding from all-causes of NVAGIB was not common and accounted for 3.5% of cirrhotic patients who underwent endoscopic therapy[16,17]. Rebleeding (usually within 30 d or 6 wk following the index endoscopy) ranged between 2%-25% (Tables 2 and 4). Rebleeding was usually managed endoscopically and salvage therapy using arterial embolisation or surgery was undertaken in very few cases (n = 8). Mortality ranged between 3%-40%, although follow-up was variable, and it was usually associated with liver function deterioration and other organ failure or infections rather than uncontrolled bleeding. Endoscopic treatment-related complications were extremely rare (n = 1).

Peptic ulcer disease

Overall, 7 studies including a total of 947 (range 29-235) patients with cirrhosis and NVAUGIB were identified (Table 2)[18-24]. Peptic ulcer disease (PUD) was the aetiology of NVAUGIB in 799 patients (311 with duodenal ulcer, 438 with gastric ulcer, 39 with both duodenal and gastric ulcers, 8 with oesophageal ulcer and 3 with stomal ulcer). Most patients (686/947) required endoscopic therapy. The most common endoscopic modality used to control bleeding was combination of epinephrine injection with coagulation or hemoclips (198 patients). Data for failure to control bleeding at the index endoscopy were available in 4 studies (30 patients) and ranged between 1.3% and 10% (median 7.5%) (Table 2). Rescue therapy was not common (Table 2). Rebleeding rates were examined in all studies and occurred in a total of 121/947 (12.7%) patients (range 1.9%-22.4%). In-hospital mortality data were available in 4 studies and reached a total of 112/698 (16%) patients (range 13.8%-17.6%). Three studies examined 6-wk or 30-d mortality which was found to be 14.5% (36/249 patients) (range 3%-17%).

GAVE

Seven studies were identified reporting the outcomes and endoscopic modalities used in a total of 128 patients with AUGIB due to GAVE of whom 47 were cirrhotics (Table 3). The most common endoscopic modality used was APC in a total of 86/128 patients. Regardless of the endoscopic modality, sessions needed to achieve eradication of GAVE and/or improvement of symptoms ranged between 1 and 10, although recurrence of GAVE was documented in most patients (Table 3). The most common outcomes reported were need for blood transfusions before and after endoscopic treatment, eradication of GAVE and treatment complications as well as mortality. Four studies reported reduction in transfusion units needed after endoscopic treatment[25-28]. Three studies reported no treatment-related complications whereas Fuccio *et al*[28] reported abdominal discomfort or pain in almost all patients which ceased spontaneously and Sato *et al*[29] a post-treatment bleeding ulcer. Mortality during follow-up was available in four studies (ranged between a mean/median of 6 and 25 mo) and reached a total of 26/74 (35%) patients of whom 4 died due to uncontrolled bleeding[25,27-29].

Table 1 Main characteristics of all included studies

Ref.	Type of study	Period of enrolment, years	Number of patients[1]	Number of cirrhotic patients with acute NVGIB	Non-variceal bleeding source	Endoscopic treatment modality	Main outcomes
Paquet *et al* [30]	Retrospective	1985-1987	339	53	MWS	EIS (polidocanol)	CoB
Baettig *et al* [35]	Retrospective	1984-1991	480 (28 with Dieulafoy's lesion)	3	DL	EI + EIS (polidocanol)	CoB; Rebleeding; Mortality
Labenz *et al* [25]	Retrospective, case series	NR	5	3	GAVE	Nd-YAG LC	CoB; Post treatment TU (median f/up 8 mo)
Schuman *et al*[31]	Retrospective	1985-1990	42	14	MWS	BICAP electrocoagulation, Epinephrine injection	CoB; Severity of bleeding in relation to liver disease and/or PH[2]
Ikeda *et al* [16]	Retrospective	1993-1996	5	4	GAVE	EC or HPC	CoB; Eradication of GAVE; Endoscopic pattern and development of GAVE
Dulai *et al* [26]	Prospective	1991-1999	744 (26 with GAVE)	7	GAVE	Bipolar EC, HPC, APC	Hct pre- and post-treatment; TU needed; Number of hospitalizations pre- and post-treatment (median f/up 6 mo)
Cheng *et al* [36]	Retrospective	1999-2001	1393 (29 with DL)	5	DL	EI, EIS, HPC	CoB; Rebleeding; Mortality
Sato *et al*[17]	Retrospective	2001-2003	8	5	GAVE	APC	Recurrence of GAVE (mean f/up 28 mo); CoT (mean f/up 28 mo)
Higuchi *et al* [32]	Prospective	1998-2005	37	11	MWS	EBL	CoB; Rebleeding (28 d)
Lecleire *et al* [27]	Retrospective	2001-2005	30	11	GAVE	APC	CoB; GAVE pattern; Recurrence of symptoms (median f/up 20 mo); CoT (median f/up 20 mo)
Seo *et al*[18]	Retrospective multicenter	May-October 2005	464	76	GU, DU, OS	EC	CoB; Rebleeding (42 d); Mortality (42 d)
Lecleire *et al* [33]	Prospective	2001-2008	218	7	MWS	EBL or EI + HC	CoB; Rebleeding; TU needed; Mortality
Fuccio *et al* [28]	Prospective	2002-2006	20	4	GAVE	APC	Resolution of transfusion dependent anemia (mean f/up 25 mo); CoT (mean f/up 25 mo)
González-González *et al*[22]	Prospective	2000-2009	160	160	GU, DU, OS	BICAP EC, EI	CoB; Rebleeding; Mortality (in-hospital)
Gad *et al*[37]	Retrospective	2007-2011	77	77	PHC, OS	APC	CoB; PHC prevalence; PHC endoscopic pattern
Awad *et al* [38]	Prospective	2009-2010	120	120	Hemorrhoids	EBL, EIS (ethanolamine or N-butyl cyanoacrylate)	CoB; HR; Rebleeding; Pain relief; Patient's satisfaction
Rudler *et al* [23]	Prospective	2008-2011	203	29	PU	EI, HC	CoB; Rebleeding; Mortality (30 d); RT
Sato *et al*[29]	Retrospective	NR	34	13	GAVE	APC, EBL	CoB; Rebleeding; Mortality; GAVE recurrence
Smith *et al* [34]	Retrospective, case series	NR	4	4	PHG, PHC	Hemospray	CoB; CoT

Morsy *et al* [24]	Prospective	2011-2012	532	93	GU, DU, OS	EI, APC	Early rebleeding (24 h after stabilising patient); Mortality (in-hospital)
Yang *et al* [19]	Retrospective	2007-2013	210	210	PU	EI, APC, HC	CoB; Rebleeding; Mortality (in-hospital); Infection (in-hospital); Length of hospital stay
Kuo *et al*[20]	Retrospective	2008-2014	235	235	PU	EI, APC, HC	CoB; Rebleeding; Mortality (in-hospital); Infection (in-hospital); Length of hospital stay
Ardevol *et al* [21]	Retrospective multicenter	2005-2012	790	144	PU	EI, Multipolar EC, HC, EIS	CoB; Rebleeding (1-45 d); Mortality (45 d, 1 year); RT

[1]Including cirrhotics and non-cirrhotics with acute non-variceal gastrointestinal bleeding and cirrhotics with obscure gastrointestinal bleeding;
NR: Not reported; MWS: Mallory-Weiss syndrome; DL: Dieaulafoy's lesion; GAVE: Gastric antral vascular ectasia; PHC: Portal hypertensive colopathy; PHG: Portal hypertensive gastropathy; LC: Lasercoagulation; APC: Argon plasma coagulation; EBL: Endoscopic band ligation; EIS: Endoscopic injection sclerotherapy; EI: Epineprhine injection, HPC: Heater probe coagulation; CoB: Control of bleeding; TU: Transfusion units; PH: Portal hypertension; Hct: Hematocrit; CoT: Complications of treatment; PU: Peptic ulcer; GU: Gastric ulcer; DU: Duodenal ulcer; OS: Other sources; HR: Hemorrhoids recurrence; RT: Rescue therapies.

Table 2 Main characteristics of studies including patients with cirrhosis and acute upper gastrointestinal bleeding due to peptic ulcers

Ref.	Patients (*n*)	Cirrhotic patients with NVAGIB (*n*)	Non-variceal bleeding source: peptic ulcer/other (*n*)	Patients received endoscopic treatment (*n*)	Endoscopic treatment modality (*n*)	Failure to control bleeding, *n* (%)	Rebleeding, *n* (%)	Mortality, *n* (%)	Rescue therapy
Seo *et al* [18]	464	76	GU: 48; DU: 16; OL: 12	48	EC: 20[1]	1/76 (1.3%)	2/76 (2.6%)	42 d: 11/76 (14.5%)	NR
González-González *et al*[22]	160	160	GU: 39; DU: 33; GU + DU: 9; EU: 3	43	EI: 7; BICAP EC: 6; CT: 30	NR	3/160 (1.9%)	In-hospital: 22 (13.8%)	S: 0
Rudler *et al*[23]	203	29	DU: 19; GU: 7; MU: 3	20	EI: 9; EI + HC: 11	NR	2/29 (7%)	30 d: 1/29 (3%)	AE: 3; S: 0
Morsy *et al*[24]	532	93	DU: 25; EU: 5; GU: 3	42	EI: 23; APC: 19	NR	4/93 (4.3%)	In-hospital: 13/93 (14%)	NR
Yang *et al* [19]	210	210	GU: 133; DU: 66; GU + DU: 11	210	EI: 80; APC: 41; HC: 13; EI + APC: 36; EI + HC: 40	7 (3.3%)	47 (22.4%)	In-hospital: 37/210 (17.6%)	NR
Kuo *et al* [20]	235	235	GU:146; DU: 73; GU + DU: 16	235	EI: 84; APC: 50; HC: 20; CT: 81	8 (3.4%)	48 (20.4%)	In-hospital: 40/235 (17%)	NR
Ardevol *et al*[21]	790	144	DU: 79; GU: 62; SU: 3	88	EI: NR; Multipolar EC: NR; HC: NR; EIS: NR	14 (10%)	15 (10%)	6 wk: 24/144 (17%)	SET: 11; AE: 3; S: 2

[1]Endoscopic treatment modality only mentioned for 20/48 patients;
NVAGIB: Non-variceal acute gastrointestinal bleeding; GU: Gastric ulcer; DU: Duodenal ulcer; EU: Esophageal ulcer; OL: Other lesions; MU: Multiple ulcers; EC: Electrocoagulation; EI: Epinephrine injection; HC: Hemoclips; CT: Combination therapy; APC: Argon plasma coagulation; EIS: Endoscopic injection sclerotherapy; NR: Not reported; S: Surgery; AE: Arterial embolisation; SET: Second endoscopic treatment.

The largest study by Sato *et al*[29] retrospectively compared APC and EBL for the treatment of GAVE (Table 3). On endoscopy, eight active bleeders were identified in the APC group and five in the EBL group and they were all successfully managed. Recurrence rates of GAVE were significantly higher in the APC group ($P < 0.05$). No endoscopy-related complications were observed apart from one patient in the EBL group who had a bleeding ulcer successfully treated with APC.

MWS

Information regarding endoscopic management in cirrhotic patients with AUGIB due to MWS is scanty.

Table 3 Main characteristics of studies including patients with cirrhosis and acute upper gastrointestinal bleeding due to gastric antral vascular ectasia

Ref.	Patients (*n*)	Cirrhotic patients with overt bleeding (*n*)	Patients received endoscopic treatment (*n*)	Endoscopic treatment modality (*n*)	Failure to control initial overt bleeding, *n* (%)	Endoscopic sessions needed (*n*)	GAVE eradication, *n* (%)	Mortality during follow-up, *n* (%)	Follow-up period (mo)
Labenz *et al*[25]	5	3	5	NA-YAG LC	0	2-8	0	0	2-12 (median = 6)
Ikeda *et al*[16]	5	4	5	EC: NR; HPC: NR	0	NR	0	NR	64.8 (mean)
Dulai *et al*[26]	744 (26 with GAVE)	7	26	Bipolar EC: 13; HPC: 7; APC: 6	0	Median = 3 (2-5)	0	NR	3-10 (median = 6)
Sato *et al*[17]	8	5	8	APC	0	Mean = 1.8 (1-3)	6/8 (75%)	NR	28 (mean)
Lecleire *et al*[27]	30 (17 cirrhotics)	11	30	APC	0	Mean = 2.2	NR	9/17 (53%)	Cirrhotics: 20 (median); Non-cirrhotics: 24 (median)
Fuccio *et al*[28]	20	4	20	APC	0	Median = 3 (1-10)	14/20 (70%)	8/20 (40%)	1-47 (mean = 25)
Sato *et al*[29]	34 (32 cirrohtics)	13	34	APC (22); EBL (12)	0	APC: Mean = 2.3 (1-3); EBL: Mean = 3 (2-4)	APC: 7/22 (32%); EBL 11/12 (92%)	9/34 (26%)	APC: 16.6 (mean); EBL: 14.6 (mean)

GAVE: Gastric antral vascular ectasia; LC: Lasercoagulation; EC: Electrocoagulation; NR: Not reported; HPC: Heater probe coagulation; APC: Argon plasma coagulation; EBL: Endoscopic band ligation.

Table 4 Main characteristics of studies including patients with cirrhosis and acute upper gastrointestinal bleeding

Ref.	Patients (*n*)	Patients with MWS bleeding (*n*)	Cirrhotic patients with MWS bleeding (*n*)	Patients with MWS received endoscopic treatment (*n*)	Endoscopic treatment modalities (*n*)	Failure to control initial overt bleeding, *n* (%)	Rebleeding, *n* (%)	Mortality during follow-up, *n* (%)
Paquet *et al* [30]	339	55	53	53	ES (polidocanol)	0	NR	NR
Schuman *et al*[31]	79	42	14	4	EI; BICAP EC	0	NR	3/42 (7%)
Higuchi *et al*[32]	37	37	11	37	EBL	0	1/37 (2.7%)	1/37 (2.7%)
Lecleire *et al* [33]	218	218	7	56	EBL: 27; EI + HC: 29	0	5/56 (9%) (Hemoclips + Epinephrine)	0
González-González *et al*[22]	160	18	18	0	EI: 0; BICAP EC : 0	NR	NR	22/160 (13.8%)

ES: Esophageal sclerotherapy; EI: Epinephrine injection; EC: Electrocoagulation; NR: Not reported; EBL: Endoscopic band ligation; HC: Hemoclips.

Four studies exclusively examined MWS as the source of bleeding and included a total of 103 cirrhotic patients[30-33] (Table 4). Paquet *et al*[30] examined 55 patients with MWS of whom 53 cirrhotics and successfully applied sclerotherapy with polidocanol into the oesophageal wall to control bleeding. In a prospective study Higuchi *et al*[32] included 37 patients with MWS of c 11 cirrhotics. They achieved initial hemostasis in all patients using endoscopic band ligation. One cirrhotic patient experienced rebleeding within 24 h and died. No other complications during or after endoscopic treatment were reported and no further bleeding during follow up period (1-24 mo). In a comparative prospective study

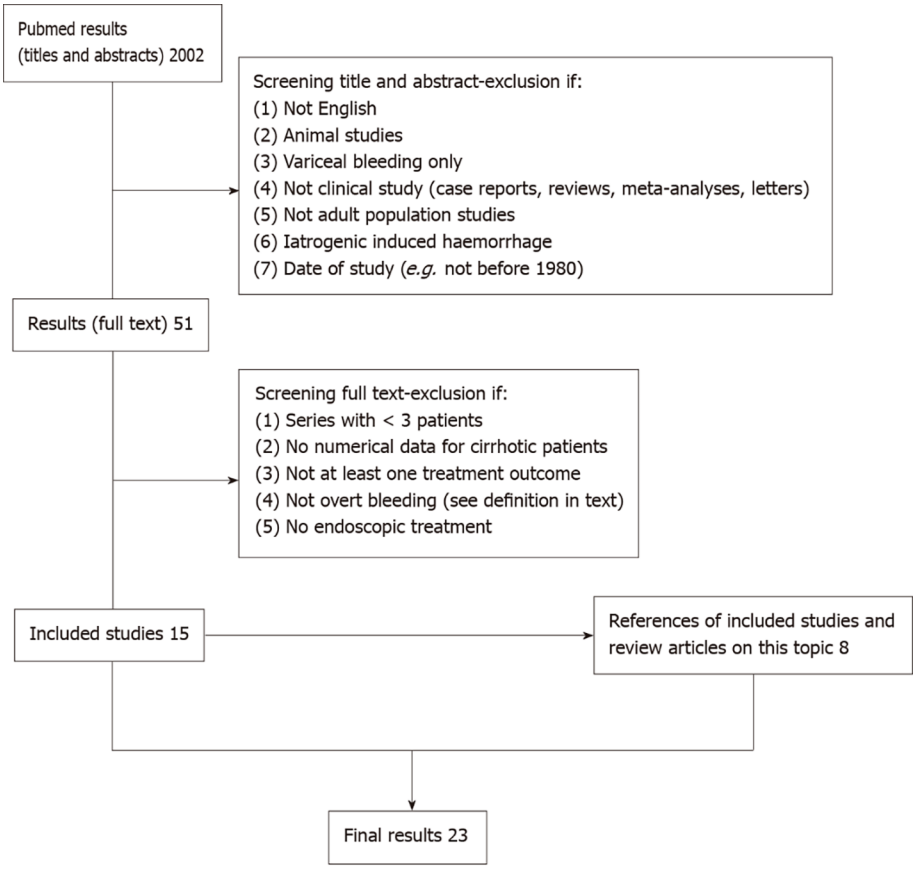

Figure 1 Flow chart of the selection of studies eligible for data extraction.

Lecleire *et al*[33] examined the efficacy of endoscopic band ligation *vs* epinephrine injection plus hemoclip and observed higher rebleeding rates in the latter group (0% *vs* 18%, $P = 0.02$).

PHG

Data on acute bleeding due to PHG and endoscopic therapy are limited. Three studies were identified including a total of 50 cirrhotic patients with acute PHG bleeding[22,24,34]. In one of them, all patients were managed conservatively but outcomes for these patients were not extractable[22]. Morsy *et al*[24] included 93 cirrhotic patients with AUGIB of whom 24 patients with acute bleeding due to PHG. They used epinephrine injection or APC in 42/93 patients with rebleeding rates reaching 4% and in-hospital mortality 14%. In a case series Smith *et al*[34] succesfully used hemospray to control acute bleeding from PHG in 3 patients of whom one had perforation and died 4 d after endoscopy.

DL

AUGIB due to DL is not common and therefore available data are extremely limited. From the studies included in this review González-González *et al*[22] reported one patient with DL who did not receive endoscopic treatment. Two studies fulfilled the inclusion criteria for our review with a total of 57 patients with bleeding DL of whom only 8 cirrhotics[35,36]. Four received epinephrine plus polidocanol injection[35] with the remaining receiving epinephrine injection plus heater probe ($n = 1$[36]), epinephrine injection monotherapy ($n = 1$[36]) or histoacryl injection ($n = 3$[36]) in all cases with initial success and without any reported rebleeding from the same lesion.

Lower acute GIB

Data with regard to lower acute GIB in cirrhotic patients are very scanty. Only two studies that investigated endoscopic therapy of acute bleeding from the lower gastrointestinal tract in patients with cirrhosis were identified[37,38]. In a retrospective series of cirrhotics with hematochezia[37], 7/77 (10%) had PHC-related bleeding. All received endotherapy with APC, achieving initial hemostasis. Moreover 12/77 (16%) patients had polyp-associated bleeding which was controlled with excision polypectomy. Other sources of LAGIB were non-specific (12%) and infectious colitis (34%), ulcerative colitis (9%), hemorrhoids (13%), rectal cancer (4%), colonic adenocarcinoma (4%) and diverticulosis (4%), and patients did not receive any specific endoscopic treatment.

Awad *et al*[38] prospectively compared endoscopic injection sclerotherapy (EIS) with endoscopic endoscopic band ligation (EBL) for the management of bleeding hemorrhoids in 120 cirrhotic patients equally divided into the two groups. Both techniques were effective in the control of bleeding with rebleeding rates reaching 10% and 13% respectively. Rebleeding was successfully managed with repeated sessions of the initial therapy (in total, 13 patients had 2 sessions while another needed 3 sessions). On average 3 bands were used for obliteration of hemorrhoids (range 2-4 bands). Recurrence of hemorrhoids did not differ significantly and occurred in 27% for the EIS group *vs* 18% in the EBL group. EBL seemed to be safer than EIS for patients with advanced cirrhosis as higher Child-Pugh score in the EIS group was correlated with rebleeding, recurrence and abscess formation. The EIS was subdivided into two groups comparing ethanolamine oleate (30 patients) and cyanoacrylate (30 patients). The former was significantly associated with lower rebleeding rates but higher pain score[38].

DISCUSSION

The main finding of the current systematic review is that endotherapy seems to be an efficient means to control hemorrhage in cirrhotics, although data especially with regard to lower bleeding, are limited. Failure to control bleeding from all-causes of NVAGIB was not frequent and accounted for approximately 3.5% of cirrhotic patients. Rebleeding (range 2%-25%) and mortality (range 3%-40%) rates were heterogenous between the studies which may be due to the different case mix, in terms of source of bleeding, endoscopic modality used, duration of follow-up patient age, cirrhosis severity *etc.*

Although variceal bleeding is the main cause of AUGIB in cirrhotic patients, published data have shown that NVGIB is not uncommon and is responsible for almost one fifth of all-cause bleeding episodes in these patients[4-7]. To our knowledge, this is the first systematic review focusing on all-cause of acute gastrointestinal bleeding in cirrhosis. A single previous review performed in 2012 including not only acute but also chronic obscure bleeding[8] while another non-systematic review from 1996 focused on NVAGIB and did not include data on lower gastrointestinal bleeding in these patients [39].

Comparative data on the utility of endoscopic therapy in AUGIB between cirrhotics and non-cirrhotics are scarce. In a prospective study Rudler *et al*[23] examined the aetiology of PUD and outcomes between cirrhotics and non-cirrhotics admitted in the intensive care unit due to PUB. Prognosis, in terms of rebleeding, need for salvage therapy, and mortality, was not different between the groups. Lecleire *et al*[27] compared cirrhotics and non-cirrhotics treated with APC due to bleeding GAVE. Patients with liver cirrhosis had overt bleeding more often (P = 0.01) and a honeycomb appearance of GAVE compared to non-cirrhotics who had a watermelon appearance. On the other hand non-cirrhotic patients required more APC sessions to achieve a stable haemoglobin level (P = 0.04). GAVE related bleeding was also examined by Dulai *et al*[26] in 26 patients of whom 7 cirrhotics and observed that portal hypertension was related to more diffuse gastric lesions and a higher chance of active bleeding during endoscopy. Obliteration of GAVE lesions was not achieved in any patient whether cirrhotic or not. Schuman *et al*[31] retrospectively compared cirrhotics and non-cirrhotics with bleeding MWS. Fourteen cirrhotic patients were identified of whom three with active bleeding during endoscopy and were successfully managed with epinephrine injection and/or BICAP electrocoagulation. Cirrhotics needed more transfusion units than non-cirrhotics whereas no correlation between MWS and the severity of portal hypertension was observed. They experienced 3/42 deaths, none related to MWS bleeding. Thus, it is clear that further studies with appropriate non-cirrhotic controls are warranted to clarify whether endoscopic therapy outcomes are comparable between cirrhotics and non-cirrhotics with acute gastrointestinal bleeding.

Studies that included unselected patients with cirrhosis and AUGIB, *i.e.*, with various causes of bleeding, showed that the most common non-variceal cause was PUD[18,22,24]. This is in accordance with other large studies which demonstrated that PUD accounts for 40%-50% of NVAUGIB in cirrhotic patients[4-7]. PUD have a higher prevalence in patients with cirrhosis compared to non-cirrhotics; in a large Swedish study[40] the overall prevalence of PUD in the general population was 4.1%, whereas in the cirrhotic population there is a significantly higher prevalence of PUD ranging from 20% to almost 50%[41-44]. Moreover, the prevalence of helicobacter pylori is similar between cirrhotics and non-cirrhotics however it does not seem to play a significant role in the development of PUD and its eradication does not seem to decrease the recurrence rate of PUD in these patients[43-47]. It has also been proposed that the more severe liver cirrhosis is, the more increased is the risk for development, recurrence, and complications of PUD[41]. Thus, it has been proposed that physiopathologic mechanisms implicated in the development of peptic ulceration in cirrhosis may differ from those in non-cirrhotic patients; congestive gastropathy and decreased gastric mucosal blood flow, impaired gastric mucus-bicarbonate barrier and epithelial renewal as well as low prostaglandin levels are some of the proposed mechanisms[45,48]. Treatment of PUB in cirrhosis is the same as in the general population. Combination of pharmacologic and endoscopic therapy namely intravenous proton pump inhibitors combined with endoscopic epinephrine injection plus a second hemostasis modality (contact thermal, mechanical or sclerosant therapy) is used to control active bleeding ulcers[49]. Notwithstanding the

same therapeutic management there are important differences compared to the general population as cirrhotics have a four-fold risk of PUB compared to controls and require endoscopic hemostasis more frequently than non-cirrhotics[4,50]. Furthermore, the risk for recurrence of PUB in the long-term and the 90-d mortality after hospitalisation for PUB are increased compared to the general population[51,52].

Published data on the comparative utility of endoscopic therapy in cirrhotics with variceal *vs* with non-variceal bleeding are also very few and somewhat conflicting. A retrospective multicenter study from Korea[18] showed that 6-wk rebleeding rate for NVAUGIB (9.3%) as well as six-week mortality rate (14.5%) were not significantly different from variceal bleeding in cirrhosis. However, comparative data between only PUB and variceal bleeding in these patients available in another retrospective multicenter study[20], demonstrated that rebleeding rates were significantly lower for PUB (10%) than variceal (26%) bleeding, but the 6-wk and 1-year risk of mortality were similar between the two groups.

Published data on the occurrence and endoscopic management of lower acute gastrointestinal bleeding in cirrhosis are very limited, based mainly on case reports, without any multicentre or comparative studies with non-cirrhotics available. Moreover in order to offer the optimal endoscopic and pharmacologic management in this group of patients it is imperative to understand the possible relation of portal hypertension with the cause of bleeding. Although PHC is a well-recognised condition that may be related to lower gastrointestinal bleeding, there is controversy in the literature concerning the relation of portal hypertension with PHC, hemorrhoids and rectal varices[53-57]. A relation between PHC and higher Child-Pugh class as well as history of esophageal band ligation or sclerotherapy has been demonstrated[37]. Hemorrhoids on the other hand seem to be more common in the absence of PHC[37]. Awad *et al*[38] reported that 75/120 (62%) of cirrhotic patients with bleeding hemorroids also had grade II or III oesophageal varices but they do not report how many of their patients had rectal varices or PHC.

One of the major limitations of our review is that data regarding cirrhotics with acute gastrointestinal bleeding are often extracted from cohorts which include non-cirrhotics, therefore cirrhosis-specific outcomes may not be readily available. Furthermore, most studies identified by the current research strategy were retrospective and single-centre and they usually included only few cirrhotic patients. Moreover, most studies did not have a non-cirrhotic control group, while rebleeding and mortality cases could frequently not be traced back to the bleeding source and endoscopic modality used. Last but not least, follow-up times and definitions of events, such as rebleeding, were heterogenous among studies.

CONCLUSION

NVAGIB is a non-negligible cause of morbidity and mortality in patients with cirrhosis and early recognition and endoscopic management are of pivotal importance. However data on most sources of NVAGIB and the efficacy of endoscopic therapy in cirrhosis are very limited, while similar data on acute bleeding from the lower gastrointestinal tract are almost non-existent in this group of patients. Our review highlights that endoscopic therapy seems to be effective in these patients, although comparative data with non-cirrhotic patients are very few. Furthermore, it is conceivable that NVAGIB may be related to decompensation of liver cirrhosis but outcomes such as hepatic encephalopathy, new-onset of ascites, and jaundice, were not available in most included studies. Although variceal bleeding is a well-investigated event in the natural history of liver cirrhosis, it is somewhat unclear whether, and to which extent, non-variceal bleeding may signify worse prognosis of these patients. Hopefully this review may stimulate further research on this subject and help clinicians administer optimal endoscopic therapy for cirrhotic patients.

ARTICLE HIGHLIGHTS

Research background

Non-variceal acute gastrointestinal bleeding (NVAGIB) accounts for approximately one fifth of the bleeding episodes in cirrhotic patients and can lead to catastrophic consequences with high morbidity and mortality. Available data and trials addressing the efficacy of endoscopic modalities used to treat NVAGIB are very limited.

Research motivation

Variceal bleeding is a well-known cause of decompensation in cirrhotic patients and endoscopic treatment and outcomes after such an episode have been well studied. Whether NVAGIB is related to decompensation and if it indicates worse prognosis in the natural history of cirrhotics still needs to be clarified. Knowledge of endoscopic treatment efficacy and outcomes is a prerequisite in answering these challenging questions. Addressing these issues can lead to future changes in treatment and follow up of these patients.

Research objectives

To analyse the different causes of NVAGIB and their frequency as well as the endoscopic modalities used to achieve haemostasis. To investigate if NVAGIB denotes worse prognosis in the natural history of cirrhotic patients, if endoscopic treatment is efficient and what are the rebleeding and failure rates of endotherapy. Data on these issues may stimulate future research, and assist clinicians in choosing the best endoscopic modality to treat NVAGIB in cirrhotics.

Research methods

A systematic review using the PRISMA statement for reporting systematic reviews and meta-analyses was conducted. The MEDLINE was searched through PubMed by two authors (Demetriou G, Augoustaki A) independently for relevant studies from 01/01/1980 until 01/01/2021 using the following query: "Liver Cirrhosis" AND "Gastrointestinal Hemorrhage/therapy". After applying exclusion/inclusion criteria 23 studies out of 2002 were chosen to be analyzed.

Research results

A total of 23 studies (15 retrospective and 8 prospective) included a total of 1288 patients with liver cirrhosis and NVAGIB of whom 958 underwent endoscopic treatment. Causes of NVAGIB in a decreasing frequency order were as follows; peptic ulcers, portal hypertensive gastropathy, gastric antral vascular ectasia, Mallory-Weiss syndrome, Dieaulafoy lesions, portal hypertensive colopathy, and hemorrhoids. Failure to control bleeding from all-causes of NVAGIB accounted for 3.5% of cirrhotic patients who underwent endoscopic therapy while rebleeding and mortality rates varied among studies (2%-25% and 3%-40% respectively). Endoscopic treatment related complications were rare (n = 1).

Research conclusions

NVAGIB is an important cause of morbidity and mortality in patients with cirrhosis and prompt diagnosis and endoscopic management affect prognosis. Despite limited data it seems that endoscopic management for upper-and lower-NVAGIB is safe and efficacious. The relatively high rebleeding and mortality rates are probably due to study heterogeneity but firm conclusions may not be drawn.

Research perspectives

The assumption that NVAGIB may be related to decompensation of liver cirrhosis and poor prognosis still need to be addressed. Expectantly this review will motivate further research on this subject and assist in administering optimal endoscopic therapy to patients with liver cirrhosis.

FOOTNOTES

Author contributions: Kalaitzakis E conceived the idea of the topic and designed the project with Demetriou G; Demetriou G and Augoustaki A searched and screened the titles and abstracts of all relative studies and then full text of the most relevant ones for eligibility criteria; any disagreement was resolved by means of consensus with all authors; all authors contributed to the selection of the studies and interpretation of the results; Demetriou G and Kalaitzakis E wrote the manuscript while Augoustaki A aided in revision; all authors discussed the results and made comments on the manuscript.

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CASE REPORT

Mucosa-associated lymphoid tissue lymphoma in the terminal ileum: A case report

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Abstract

BACKGROUND

The lymphoma of the mucosa-associated lymphoid tissue (MALT) is predominantly found in the stomach. The few cases reported in the literature of MALT lymphomas affecting the ileum are in patients who are already symptomatic and with clear advanced endoscopic findings. We present the first case of an asymptomatic female patient who underwent colonoscopy as a routine examination with the findings of an ulcer in the distal ileum region, which histopathological examination and associated immunohistochemistry revealed the diagnosis of MALT lymphoma.

CASE SUMMARY

A 57-year-old asymptomatic female patient underwent a colonoscopy exam for screening. The examination revealed an ulcer of medium depth with well-defined borders covered by a thin layer of fibrin and a halo of hyperemia in the distal ileum portion. Findings are nonspecific but may signal infections by viruses, protozoa, and parasites or inflammatory diseases such as Crohn's disease. Biopsies of the ulcer were taken. The anatomopathological result revealed an atypical diffuse lymphocytic infiltrate of small cells with a characteristic cytoplasmic halo of marginal zone cells. The immunohistochemical study was performed and the results demonstrated a negative neoplastic infiltrate for the

expression of cyclin D1 and cytokeratin AE1/AE3 and a positive for BCL60 in the germinal center. The test also revealed CD10 positivity in the glandular epithelium and germinal center of a reactive follicle with dual-labeling of CD20 and CD3 demonstrating the B lymphocyte nature of the neoplastic infiltrate. In BCL2 protein labeling, the neoplastic infiltrate is strongly positive with a negative germinal center. The findings are consistent with immunophenotype B non-Hodgkin's lymphoma, better classified as extranodal MALT. The patient was treated with chemotherapy and showed complete regression of the disease, as evidenced by colonoscopy performed after treatment.

CONCLUSION
MALT lymphomas in the terminal ileum are extremely rare and only 4 cases have been reported in the literature. Given the low sensitivity and specificity of endoscopic images in these cases, the pathology can be confused with other important differential diagnoses such as inflammatory diseases or infectious diseases and which makes the biopsy important, even in asymptomatic patients, paired with anatomopathological analysis and immunohistochemistry which is the gold standard for correct diagnosis.

Key Words: Mucosa-associated lymphoid tissue lymphoma; Ileum; Colonoscopy; Diagnosis; Biopsy; Case report

Core Tip: Mucosa-associated lymphoid tissue (MALT) lymphoma is predominantly found in the stomach. Only a few cases of MALT lymphomas affecting the ileum have been published in the literature and these patients already had clear symptoms and endoscopic findings. We present a rare case of MALT lymphoma in the terminal ileum in an asymptomatic patient who underwent the examination for age screening.

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INTRODUCTION

Mucosa-associated lymphoid tissue (MALT) lymphoma is a low-grade B-cell neoplasm of the extranodal marginal zone characterized by a lymphoid infiltrate in the mucous layer of hollow organs and glandular tissues[1,2]. The gastrointestinal tract is involved in about 50% of the cases[2,3] with the stomach accounting for 85% of all cases and strongly related to the presence and infection by *Helicobacter pylori* (*H. pylori*)[1,4]. Other, less usual regions can also be affected, such as salivary glands, lungs (14%), head and neck (15%), ocular attachments (12%) and skin (11%)[5].

MALT lymphomas in the ileum are extremely rare and few cases have been reported in the literature [5-9]. In these, all patients had already presented with an advanced degree of involvement with notable symptoms and with lesions dispersed throughout the ileocecal region[5,6].

This is the first reported case of a terminal ileum MALT lymphoma in an asymptomatic patient reported in the literature.

CASE PRESENTATION

Chief complaints

Asymptomatic.

History of present illness

A 57-year-old asymptomatic female patient underwent a colonoscopy exam for screening. The examination revealed an ulcer of medium depth with well-defined borders covered by a thin layer of fibrin and a halo of hyperemia in the distal ileum portion (Figure 1). Findings are nonspecific but may signal infections by viruses, protozoa and parasites or inflammatory diseases such as Crohn's disease.

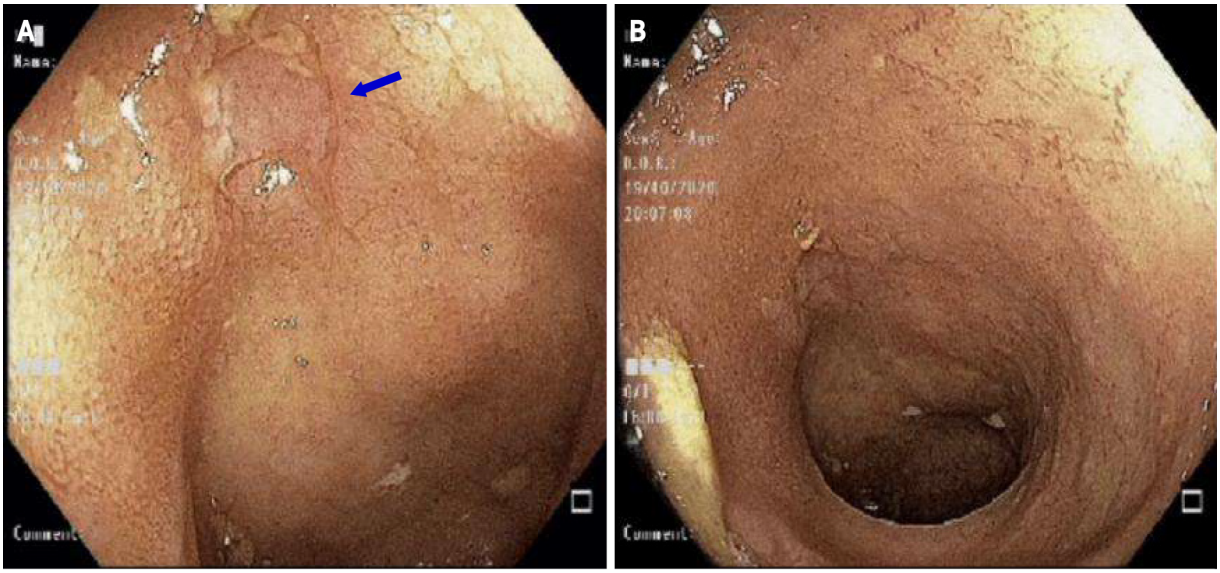

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Figure 1 Colonoscopy exam. A: Ulcer in the terminal ileum; B: Mild ulcer in terminal ileum.

Biopsies of the ulcer were taken.

The anatomopathological result revealed an atypical diffuse lymphocytic infiltrate of small cells with a characteristic cytoplasmic halo of marginal zone cells. The infiltrate presented with nodular and poorly delimited areas with dissection of collagen fibers and the muscular layer of the mucosa. There was no clear distinction regarding germinal centers. Signs of cellular atypia were also observed with enlarged nuclei. In the most superficial portion there was focal erosion, epithelial reactivity and eosinophilia (above 15 *per* high-power field) (Figure 2). No granulomas were found and there were no signs of infection by parasitic agents. An immunohistochemical study was requested to investigate lymphoproliferative disease.

The immunohistochemical study was performed by the EnVision FLEX Visualization System kit AGILENT (DAKO) method, which the results demonstrated a negative neoplastic infiltrate for the expression of cyclin D1 (Figure 2B) and cytokeratin AE1/AE3 (Figure 2C) and positive for BCL60 in the germinal center (Figure 2D). The test also revealed CD10 positivity in the glandular epithelium and germinal center of a reactive follicle (Figure 3A and B) with dual labeling of CD20 and CD3 demonstrating the B lymphocyte nature of the neoplastic infiltrate (Figure 3C and D). In BCL2 protein labeling, the neoplastic infiltrate is strongly positive with a negative germinal center (Figure 3E and F).

FINAL DIAGNOSIS

The findings are consistent with immunophenotype B non-Hodgkin's lymphoma, better classified as extranodal MALT. The identification of lymphoid proliferation with atypical limits in a nodular and infiltrative pattern with foci of epithelial aggression was crucial for the diagnosis. Since MALT lymphomas are always negative for BCL6 and CD10 and positive for BCL2 with a negative germinal center, it was possible to rule out the differential diagnosis of follicular lymphoma.

TREATMENT

The patient was referred to the oncology team and treated with chemotherapy.

OUTCOME AND FOLLOW-UP

Upon completion of treatment, the patient showed complete regression of the disease as evidenced by colonoscopy performed after treatment (Figure 4).

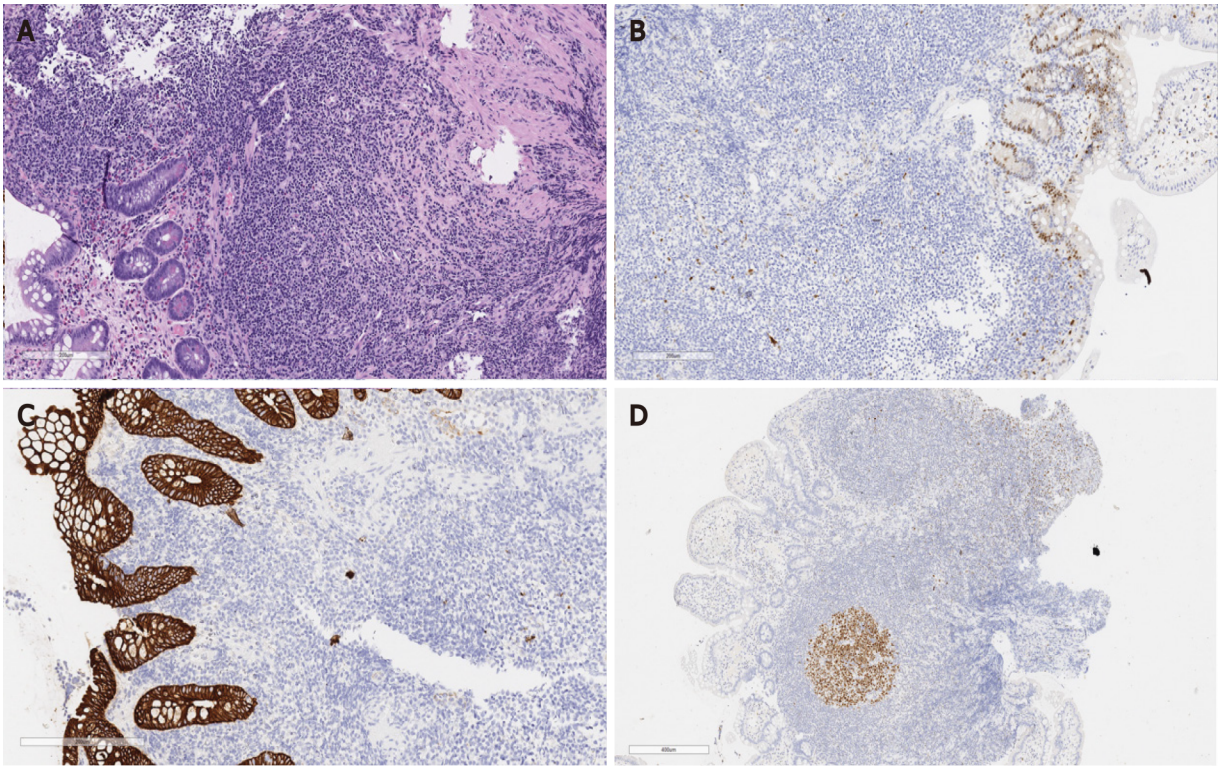

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Figure 2 Biopsy of terminal ileum showing. A: Hematoxylin & eosin-dense lymphocytic infiltrate composed of small cells, with a cytoplasmic halo, characteristic of cells in the marginal zone; B: Cyclin D1-Negative neoplastic infiltrate for protein expression of cyclin D1. Observe the positive control in the glandular epithelium; C: Cytokeratin cocktail AE1/AE3-negative neoplastic infiltrate for protein expression of cytokeratin. Observe the positive control in the glandular epithelium; D: BCL6-Protein label for BCL60. Note the negativity of the neoplastic infiltrate, and the positive internal controls in the germinal center of a reactional follicle.

DISCUSSION

Extranodal marginal zone lymphoma (MALT lymphoma) is characterized by the proliferation of small B lymphocytes[10]. The stomach is the most common site of involvement where the main etiology is *H. pylori* infection[1]. In these cases, the endoscopic findings are varied and involve polyps, ulcerations, erythematous lesions, nodules and other non-specific findings[11]. Extranodal marginal zone lymphomas that affect the ileum region are extremely rare and only a few cases have been reported in the literature[5-9]. None of the previous studies showed *H. pylori* infections so the etiology of the disease remains unknown.

Endoscopic findings of primary small bowel lymphoma can be classified into 5 patterns: Mucosal fold thickening; nodular pattern, defined by the presence of nodules and micronodules of variable sizes; infiltrative pattern, where the bowel wall is immobile, not distended by insufflation, and firm over forceps; ulcerative pattern with ulcers of variable sizes and depths, and mosaic pattern[12].

Among the four cases published in the literature on ileum MALT lymphomas, all presented endoscopic findings with multiple protuberances: Two[5,7] cases with ulcerations and two[6,8] cases with smooth mucosa. In one case, the presence of a single mass in the intestine was demonstrated without erosions in the mucosa[6].

The treatment of MALT lymphoma is initially made with the eradication of *H. pylori*, in cases with involvement of the bacteria. If there is no concomitant *H. pylori* infection or no tumor remission after *H. pylori* treatment, radiotherapy, chemotherapy, or immunotherapy with anti-CD20 monoclonal antibodies should be considered. Radiotherapy has an excellent prognosis when used in cases where the disease is localized. In the presence of disseminated or more advanced disease, the use of radiotherapy or immunotherapy is indicated. Treatment must be individualized according to the stage of the disease and symptoms, as well as the patient's preference[13]. Although MALT lymphoma has a favorable prognosis and is responsive to systematic therapy, especially when identified early, when patients are symptomatic, unfortunately they already have a more advanced degree of involvement.

Terada[5] reported the case of a 34-year-old patient with abdominal pain and melena whose colonoscopy revealed multiple nodules and ulcers scattered throughout the ileum. Endoscopic images were suggestive of ileitis, mesenchymal tumor, or lymphoma.

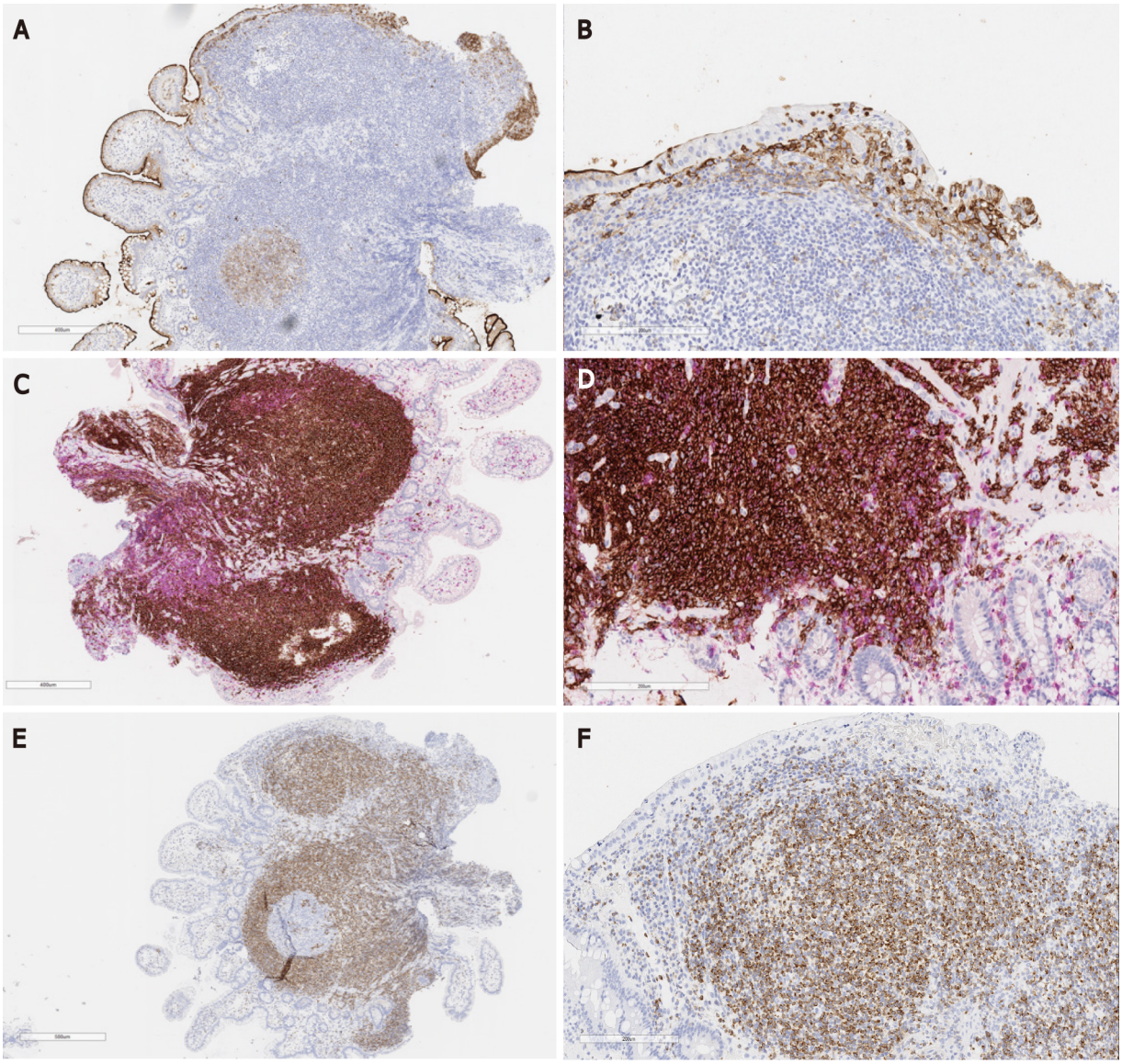

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Figure 3 Terminal ileum biopsy showing. A: Protein labeling for CD10. Note the negativity of the neoplastic infiltrate, and the positive internal controls of the glandular epithelium and germinal center of a reactional follicle; B: Protein labeling for CD10. Note the negativity of the neoplastic infiltrate and the positive internal controls of the glandular epithelium; C and D: Double labeling of CD20 (brown) and CD3 (red) demonstrating the nature of B lymphocytes of the neoplastic infiltrate. Note that T cells border the neoplastic infiltrate and preferably the epithelium, attesting to its reaction nature; E: Protein labeling for BCL2. Note that the neoplastic infiltrate expresses strongly and the internal negative control in the germinal center of a reactional follicle; F: Strong protein labeling of the neoplastic infiltrate for BCL2

Hasegawa *et al*[6] described two cases of oligosymptomatic patients with abdominal pain being a common symptom. Colonoscopy in the first case found multiple whitish nodules in the region close to the ileocecal valve, which had a smooth and polished appearance. In the second case, a colonoscopy revealed an ileocecal valve with an enlarged, soft appearance and areas of enanthema.

Makino *et al*[7] discussed a case of a patient with initial complaints of postprandial epigastric pain. Colonoscopy examination revealed multiple protruding lesions in the terminal ileum with an erosive surface covered by swollen mucosa.

In the report by Ohashi *et al*[8] colonoscopy identified multiple polyposis lesions in the terminal ileum with an absence of villi.

In all cases, biopsy with histological evaluation concurrently with immunohistochemical analysis was crucial for the diagnosis of MALT lymphoma.

The uniqueness of the case presented in this study is due to the fact that the patient was asymptomatic and her endoscopic findings had a more discrete and nonspecific pattern compared to other studies which made the diagnosis even more challenging.

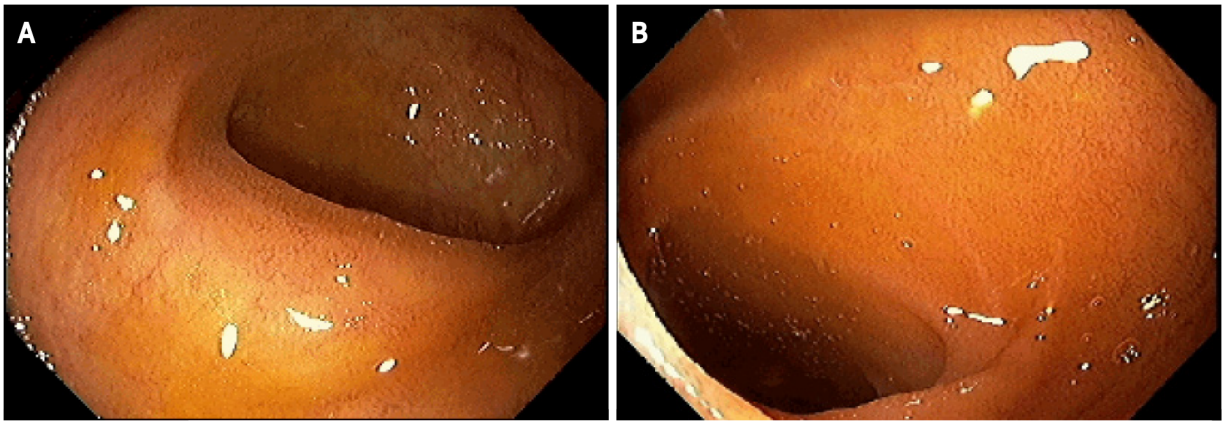

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Figure 4 Colonoscopy after treatment. A: Disease-free mucosa; B: Ulcer-free terminal ileum.

CONCLUSION

Given the low sensitivity and specificity of endoscopic images in these cases the pathology can be confused with other important differential diagnoses such as inflammatory diseases (such as Crohn's disease) or infectious diseases, which makes the biopsy, even in asymptomatic patients, with anatomo-pathological analysis and performing immunohistochemistry, the gold standard for correct diagnosis [14].

FOOTNOTES

Author contributions: de Figueiredo VLP, Ribeiro IB, and de Moura EGH performed the data curation; Ribeiro IB and de Moura DTH contributed to the formal analysis; Ribeiro IB and de Moura EGH performed the investigation; de Moura EGH contributed to the supervision; de Figueiredo VLP and Ribeiro IB contributed to the writing of the original draft; Ribeiro IB contributed to the writing of the review and editing.

Informed consent statement: The work described has been conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent for publication of this case was obtained from the patient's daughter (witnessed by two physicians).

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CASE REPORT

Z-per-oral endoscopic myotomy as definitive prevention of a bleeding ulcer in Zenker's diverticulum: A case report

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Abstract

BACKGROUND

Bleeding from Zenker's diverticulum is extremely rare. At present, there are no guidelines for the management of bleeding Zenker's diverticulum because of its rarity. Per-oral endoscopic myotomy (Z-POEM) is a precision myotomy technique and minimally invasive procedure for the treatment of Zenker's diverticulum. We present a systematic review and a rare case of bleeding Zenker's diverticulum that was effectively treated using Z-POEM.

CASE SUMMARY

A 72-year-old presented after 3 d of hematemesis. He had a 2-year history of progressive dysphagia and reported no antiplatelet, anticoagulant, or non-steroidal anti-inflammatory drug use. His vital signs were stable, and the hematocrit was 36%. Previous gastroscopy and barium swallow had revealed Zenker's diverticulum before the bleeding occurred. We performed gastroscopy and found a 5-mm ulcer with a minimal blood clot and spontaneously resolved bleeding. Z-POEM for definitive treatment was performed to reduce accumulation of food and promote ulcer healing. He had no complications and no bleeding; at the follow-up 6 mo later, the ulcer was healed.

CONCLUSION

Z-POEM can be definitive prevention for bleeding ulcer in Zenker's diverticulum that promotes ulcer healing, reducing the risk of recurrent bleeding. Z-POEM is also a definitive endoscopic surgery for treatment of Zenker's diverticulum.

Key Words: Zenker's diverticulum; Bleeding Zenker's diverticulum; Ulcer; Upper gastrointestinal bleed; Peroral endoscopic myotomy for Zenker's diverticulum; Peroral endoscopic myotomy

Core Tip: Bleeding from ulcers in a Zenker's diverticulum is extremely rare. Elderly patients with early symptoms of progressive dysphagia should be treated with a high index of suspicion. Risk factors include acidic pills, such as aspirin and non-steroidal anti-inflammatory drugs, that lodge themselves in the diverticulum creating an ulcer, and accumulation of food in the bottom of diverticulum leads to inflammation and subsequent ulcers. Per-oral endoscopic myotomy is a new definitive treatment for Zenker's diverticulum that can promote ulcer healing, decrease recurrent bleeding, and decrease dysphagia.

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INTRODUCTION

Zenker's diverticulum is a pouch of false diverticulum that forms at a point of weakness in the posterior pharyngeal wall, known as Killian's triangle, within the upper esophageal sphincter[1,2]. The overall prevalence of Zenker's diverticulum in general population is 0.10%-0.11%[3]. The typical presentation is progressive dysphagia of solid and liquid food, regurgitation, and aspiration in elderly patients. The average age of patients with Zenker's diverticulum is 70-80 years old[4]. Complications of Zenker's diverticulum include choking and aspiration pneumonia; a large diverticulum more than 4 cm in size can compress the trachea or esophagus and cause obstruction[5]. Rare complications include ulceration, bleeding, and malignant transformation (squamous cell carcinoma)[2,6]. Bleeding from a Zenker's diverticulum is rare and only six cases have been reported in the last 20 years[7-12]. Patients typically present with hematemesis and/or sometimes hemoptysis. This can be fatal as result of hemodynamic instability following massive bleeding. The ulcer is one of the risk factors of bleeding Zenker's diverticulum. To the best of our knowledge, this is the seventh reported case of a bleeding Zenker's diverticulum in the past 20 years, and no standard treatment has been established for this condition. To date, minimally invasive third-space endoscopic surgery per-oral endoscopic myotomy (Z-POEM) plays an important role in the treatment of Zenker's diverticulum[13]. We present a case report of a patient who developed upper gastrointestinal bleeding (UGIB) from a rare Zenker's diverticulum who was treated definitively using third-space endoscopic surgery, Z-POEM, and provide a systematic review of the available literature.

This case report follows the SCARE 2016 criteria. The systematic review of the literature followed the PRISMA guidelines (Figure 1). We searched the PUBMED and SCOPUS databases for articles published between 2000 and 2020 published in the English language, including case reports and original article. The search terms were "Zenker's diverticulum" OR "esophageal diverticulum" AND "bleeding." The first author screened the titles and abstracts of the identified studies to identify potentially relevant studies; full-text assessment was then performed to assess eligibility to be included. If the first author was uncertain whether a given study should be included, the corresponding author was consulted to reach a conclusion. The data were extracted and patient characteristics, such as the size of the Zenker's diverticulum, management of bleeding, definitive management of Zenker's diverticulum, follow-up length, and outcome, were collected.

CASE PRESENTATION

Chief complaints

A 72-year-old man was admitted to our hospital with a 3-day history of hematemesis.

History of present illness

The patient developed hematemesis 3 d before presenting at our hospital. The hematemesis was approximately 200 mL in volume 2 times. He was admitted to the nearest private hospital. His hematocrits was 25%. Esophagogastroduodenoscopy (EGD) under local anesthesia was performed on the first day in the previous hospital but failed because the patient choked and resisted scope insertion. He was reported to have anemia with a hematocrit 25% at the previous hospital, he received a 1-unit transfusion of red blood cells, intravenous fluids, and pantoprazole. On day 3 after admission, the patient had no

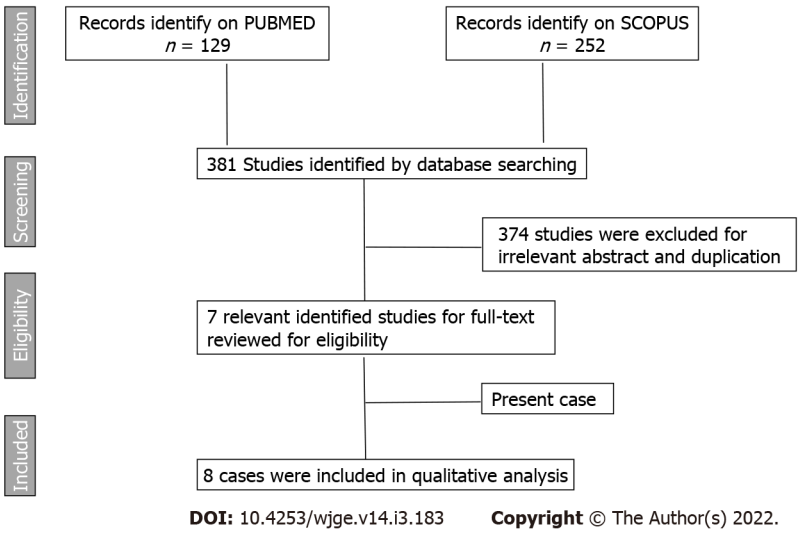

Figure 1 A study flowchart according to Preferred Reporting Items for Systematic reviews and Meta-analysis guidelines (PRISMA).

hematemesis or anemia and had a hematocrit of 36%. He was then referred to our hospital. We performed gastroscopy and found a 5-mm ulcer with minimal blood clot.

History of past illness

The patient had diabetes mellitus and primary hypertension; he took 81 mg aspirin until almost 8 mo before he developed hematemesis. He had an approximately 2-year history of progressive dysphagia, which manifest as difficulty in swallowing solid foods then liquid foods, sometimes choking, and a non-significant decrease in body weight; there was no evidence of aspiration pneumonia. Barium swallow was performed and revealed a Zenker's diverticulum that was 4 cm wide and 7.1 cm long, with a 1.1-cm-wide neck (Figure 2). Gastroscopy was performed and confirmed a large diverticulum 20 cm from the incisors without any ulcer in the diverticulum. He was diagnosed with Zenker's diverticulum and put on the waiting list for Z-POEM before developing hematemesis.

Personal and family history

No family history of Zenker's diverticulum.

Physical examination

On the day of admission, the patient was not pale and had a stable blood pressure of 146/70 mmHg and heart rate of 62 beats per minute. On physical examination, the abdomen was soft with no tenderness. Rectal examination found an empty rectum without any gross masses.

Laboratory examinations

Laboratory investigation revealed a hematocrit of 36%.

Imaging examinations

Barium swallow was performed and revealed a Zenker's diverticulum that was 4 cm wide and 7.1 cm long, with a 1.1-cm-wide neck (Figure 2B).

FINAL DIAGNOSIS

The final diagnosis was Zenker's diverticulum with a bleeding ulcer that spontaneously resolved.

TREATMENT

Because the bleeding ulcer spontaneously resolved, we decided therapeutic endoscopy of the ulcer was not necessary; however, we performed Z-POEM as definitive treatment of Zenker's diverticulum. This procedure aimed to improve dysphagia and to decrease food and drug retention in the diverticulum to reduce inflammation of the healed ulcer and prevent recurrent bleeding. Informed consent for the procedure was obtained from the patient after explaining the prognosis, results, and potential complic-

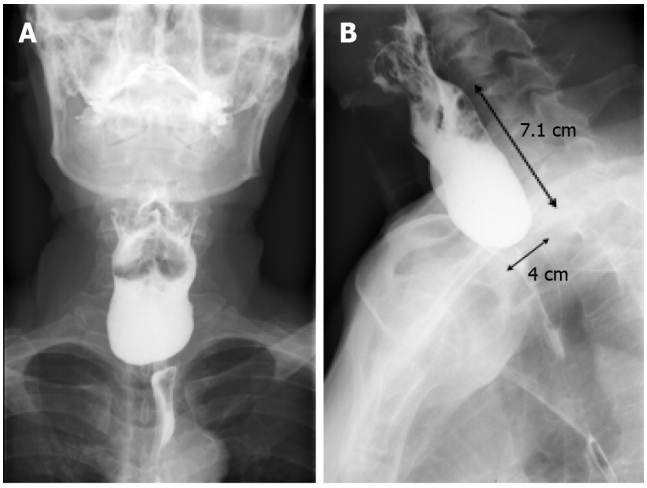

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Figure 2 Preoperative barium swallow. A: Zenker's diverticulum; B: Size 4 cm × 7.1 cm, widening 1.1 cm before develop upper gastrointestinal bleeding.

ations of the procedure, such as perforation. The Z-POEM technical process is shown in Figure 3. The operator was a surgical endoscopist in a university hospital. The patients underwent Z-POEM under general anesthesia with an endotracheal tube to prevent aspiration and end tidal CO_2 monitoring. CO_2 gas insufflation through the endoscope was required. The Z-POEM procedure was performed using a single-channel gastroscope (EG-760CT; Fuji-film Medical Co., Ltd. Tokyo, Japan). A triangle-tipped knife (KD-645; Olympus Corporation) was used for the mucosal incision, submucosal dissection, and myotomy. A small-caliber-tip transparent hood (ST hood) (DH-28GR; Fuji-film Medical Co., Ltd. Tokyo, Japan) was used to maintain and stabilize the operative field. Glycerol with a few drops of indigo carmine was used to lift the submucosal layer. The surgery was performed using a high-frequency electrosurgical energy generator (VIO 300 D; Erbe Elektromedizin, Tubingen, Germany) in endo cut mode (effect, 2.3 W) and spray coagulation mode (effect, 1,100 W). The procedure time was defined as the time from the insertion of the endoscope to application of the last through-the-scope clip (TTC). The septal muscle of Zenker's diverticulum was located 20 cm from the incisors and was 1.1 cm wide (Figure 3A). The submucosa was lifted using glycerol and indigo carmine at the septum level, and a mucosal incision was made above the septal muscle using a triangle-tipped knife in endo cut mode (effect 2.3 W) (Figure 3B). Submucosal tunneling was performed with transparent hood assistance, and submucosal dissection was performed with coagulation along both sides of the septal wall using the spray coagulation mode (effect, 1,100 W) up to behind the ulcer (Figure 3C). The submucosal layer behind the ulcer had numerous inflamed small vessels; partial coagulation of these small vessels was achieved using a Coagrasper (Figure 3D). The picture 3E shows ulcer while checking mucosal integrity after performed submucosal tunneling before undergo myotomy. After checking the integrity of the mucosa in the ulcer region, myotomy of the septal muscle was performed using endo cut mode (effect, 2.3 W) to achieve complete septal myotomy (Figure 3E-G). TTCs were applied to achieve mucosal apposition (Figure 3H). Neither patient developed bleeding or perforation. The total procedure time was 65 min.

OUTCOME AND FOLLOW-UP

Water soluble contrast esophagography was performed on postoperative day 1 to confirm the absence of leakage, and the patients were able to resume an oral diet thereafter. He had no recurrent bleeding. EGD was repeated 6 mo postoperatively because inflammation might be subside to confirm that the ulcer had resolved and that there was no food retention as shown in Figure 4. He was better able to swallow soft foods but still had some degree of difficulty with solid food; he also reported a sensation of a foreign body in his neck but no pain, hematemesis, melena, or choking. Moreover, he had a 6-kg weight gain.

DISCUSSION

Our literature search only identified six published English language case reports[7-12]. Including our present case, the average age of patients was 77.86 years, which is consistent with the average age of patients with Zenker's diverticulum[2]. The average size of Zenker's diverticulum associated with UGIB

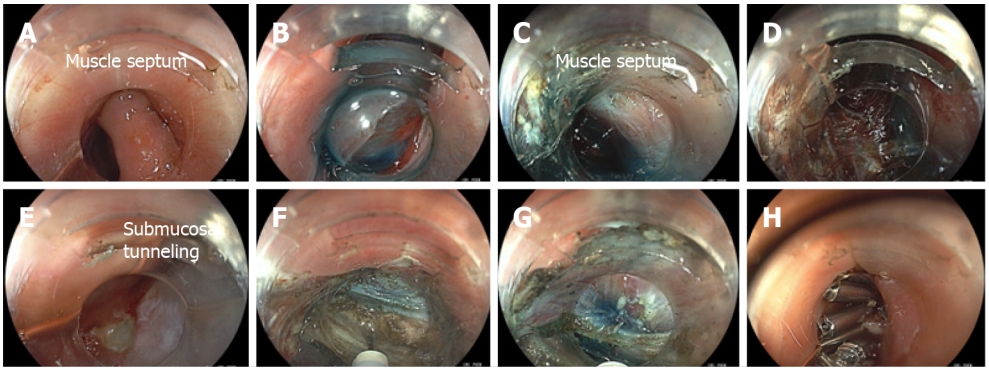

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Figure 3 Per-oral endoscopic myotomy for Zenker's diverticulum. A: Endoscopic view of the Zenker's diverticulum with muscle septum, located 20 cm from the incisors; B: The mucosal incision was performed after lifted submucosa by using glycerol with a few drops of indigo carmine injected at the septum; C: Submucosal tunneling and dissection was performed along both sides of the septal wall; D: A submucosal tunnel behind the ulcer contain many small vessel, we partially coagulate by coagrasper to stop bleeding and also avoid mucosal perforation; E: The ulcer after submucosal tunneling: The picture shows ulcer while checking mucosal integrity after performed submucosal tunneling before undergo myotomy; F and G: The myotomy was performed until the last fibers of septal muscle; H: The mucosal defect closed by through-the-scope clip.

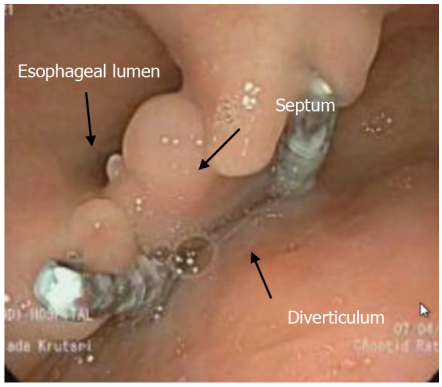

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Figure 4 The esophagogastroduodenoscopy show no recurrent ulcer and no food retention after 6 mo follow up.

is 6.325 cm as shown in Table 1. Nowaday, there was not well established whether diverticulum size is related to the occurrence of UGIB but more bigger size is prone to have pills and food accumulation then more risk development of ulcer formation and UGIB. While the pathophysiology of a bleeding diverticulum is unclear, in our review, most cases were associated with chronic inflammation and ulceration of the diverticulum[7-10,12]. Common causes of ulcer formation in the diverticulum include aspirin and non-steroidal anti-inflammatory drug tablets, which are acidic and can become lodged or trapped in the diverticulum; the prolonged contact induces direct and indirect mucosal injury. Chronic alcohol consumption, gastroesophageal reflux disease (GERD), and stimulation of acid secretion also induce ulcer formation[10,14]. Anticoagulant use induces coagulopathy, which can lead to bleeding from diverticula, with or without ulceration, similar to other types of GI bleeding. Another assumed cause of bleeding Zenker's diverticulum is chronic inflammation from food accumulation in the diverticulum inducing inflammation or infection, with or without ulceration. This assumption was confirmed by Sardana *et al*, who reported a case of bleeding Zenker's diverticulum treated using diverticulectomy with a pathology report identifying chronic inflammation as the cause of mucosal bleeding[11]. Therefore, larger diverticula are more likely to ulcerate and bleed, especially those larger than 4 cm.

Bleeding from Zenker's diverticulum is rare and can be fatal, like other causes of UGIB. Elderly patients with previous progressive or intermittent dysphagia and regurgitation must be treated with a high index of suspicion. Currently, there are no guidelines regarding the management of bleeding Zenker's diverticulum because of its rarity. Flicker *et al* and Eaton *et al* reported successfully stopping bleeding from the diverticulum using an endoscopic hemoclip[8,9]. There are two case reports of failed endoscopic treatment due to blood pooling and hemodynamic instability, which prevented insertion of the endoscope; in this emergency setting, urgent open diverticulectomy was used as treatment[7,10]. For successful endoscopic management, the neck of the diverticulum should be more than 1 cm wide so the endoscope can pass into the diverticulum for therapeutic management of bleeding at the bottom of

Table 1 Summary of previous case reports of bleeding Zenker's diverticulum, including present case

Ref.	Age (yr)	Antiplatelet or coagulant use	NSAIDs	Ulcer in diverticulum	Diverticulum size (cm)	Technique to stop bleeding	Definitive surgical treatment	Follow up (months)	Recurrent bleeding
Haas *et al* [7], 2008	71	Aspirin	No	Yes	Large	Urgent diverticulectomy Stop aspirin	Diverticulectomy	N/A	No
Flicker *et al*[8], 2010	83	Aspirin Clopidogrel	No	Yes	Large	Hemoclip	Diverticulectomy	N/A	No
Eaton *et al*[9], 2011	85	Aspirin	No	Yes	5.2	Hemoclip	Died after discharge home from heart failure	N/A	No
Bălălău *et al*[10], 2013	75	No	No	Yes	4	Diverticulectomy	Diverticulectomy	12	No
Sardana *et al*[11], 2014	89	Aspirin Warfarin	No	No	9	FFP; Stop aspirin and warfarin	Diverticulectomy and cricopharyngeal myotomy	N/A	No
House *et al*[12], 2016	70	Aspirin, Clopidogrel	No	Yes	Large	IV pantoprazole; Stop aspirin and clopidogrel	Diverticulectomy	N/A	No
Present case	72	Aspirin	No	Yes	7.1	IV pantoprazole	Z-POEM	12	No

N/A: Not available data; POEM: Per-oral endoscopic myotomy.

diverticulum. There were two case reports of bleeding stopping spontaneously after withholding anticoagulant and aspirin treatment[11,12]. As in our case, the bleeding from the ulcer in the diverticulum can stop spontaneously. Based on this evidence, endoscopic treatment may be the first choice, but if there is hemodynamic instable or endoscopic treatment fails or cannot identify the esophageal lumen, open diverticulectomy in an emergency setting is mandatory. Insertion of an endotracheal tube is recommended when endoscopic treatment is performed due to the high resistance and pooling of blood in the diverticulum leading to aspiration of blood into the pulmonary system.

After endoscopic treatment successfully stops the bleeding, definitive treatment of Zenker's diverticulum is necessary to treat the ulcer and prevent rebleeding. In emergency situations when the patient is hemodynamically unstable or endoscopic treatment fails, open diverticulectomy is mandatory *via* left lateral neck incision to excise the bleeding diverticulum immediately. Therefore, patients and their relatives should be informed of the double set-up for endoscopic management and open surgery. Open diverticulectomy leads to a good outcome in 93% of cases, but there is a high rate of complications (10.5%-30%) and mortality (3%), respectively[15-17]. Potential complications include pharyngocutaneous fistulas, mediastinitis, perforation, vocal cord paralysis, and transient recurrent laryngeal nerve paralysis[18,19].

A comparison of definitive treatment of Zenker's diverticulum with per-oral endoscopic myotomy (Z-POEM), flexible endoscopic septostomy, stapler-assisted Zenker's diverticulectomy, endoscopic harmonic scalpel, and standard open diverticulectomy found that Z-POEM allows the most precise myotomy because the operator can see until the last fiber of septal muscle[13]. Z-POEM also has a lower complication rate (6.17%) because of the postoperative intact mucosal integrity, and with precision myotomy, the bottom of the diverticulum can be seen so perforation rarely occurs[3,13]. While other procedure of treatment Zenker's diverticulum such as standard open neck diverticulectomy and flexible endoscopic septotomy had more complication rate 10.5% and 11.3%, respectively[13]. The recurrence rate following Z-POEM can be as low as 1.23%, compared with a recurrence rate of 11%-20% for other techniques[13,20-22]. In our present case, Z-POEM was a minimally invasive definitive treatment that aimed to promote ulcer healing by decreasing the accumulation of food in the diverticulum. During Z-POEM, submucosal tunnelling can identify small vessels behind the ulcer and coagulate these vessels to stop the bleeding without any perforation. This patient experienced no perforation or rebleeding. After 6 mo of follow-up, the ulcer was healed.

In summary, bleeding Zenker's diverticulum is rare and may be caused by ulceration due to acidic medications such as aspirin, NSAIDs or food retention-induced inflammation. Elderly patients with progressive dysphagia should be treated with a high index of suspicion. Therapeutic endoscopy is the

first choice to manage bleeding Zenker's diverticulum under general anesthesia with endotracheal intubation to prevent aspiration. Z-POEM is a definitive for Zenker's diverticulum treatment that allows precision myotomy, which promotes ulcer healing and reduce the risk of rebleeding by decreasing the accumulation of drugs or food in the diverticulum with a low rate of complications.

CONCLUSION

Z-POEM can be definitive prevention for bleeding ulcer in Zenker's diverticulum that promotes ulcer healing, reducing the risk of recurrent bleeding. Z-POEM is also a definitive endoscopic surgery for treatment of Zenker's diverticulum.

FOOTNOTES

Author contributions: Krutsri C and Hiranyatheb P designed, performed and wrote the paper; Sumritpradit P and Singhatas P wrote the paper and analysed the data; Choikrau P contributed analytic tools and analysed the data.

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Conflict-of-interest statement: The authors declare that they have no conflict of interest.

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The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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MINIREVIEWS

Endoscopic ultrasound guided interventions in the management of pancreatic cancer

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Abstract

There has been a growing interest in developing endoscopic ultrasound (EUS)-guided interventions for pancreatic cancer, some of which have become standard of care. There are two main factors that drive these advancements to facilitate treatment of patients with pancreatic cancer, ranging from direct locoregional therapy to palliation of symptoms related to inoperable pancreatic cancer. Firstly, an upper EUS has the capability to access the entire pancreas–lesions in the pancreatic head and uncinate process can be accessed from the duodenum, and lesions in the pancreatic body and tail can be accessed from the stomach. Secondly, there has been a robust development of devices that allow through-the-needle interventions, such as placement of fiducial markers, brachytherapy, intratumoral injection, gastroenterostomy creation, and ablation. While these techniques are rapidly emerging, data from a multicenter randomized controlled trial for some procedures are awaited prior to their adoption in clinical settings.

Key Words: Endoscopic ultrasound-guided intervention; Pancreatic cancer; Fiducials; Ablation; Intratumoral therapy

Core Tip: Interventional endoscopic ultrasound in pancreatic cancer has been developed *via* a through-the-needle fashion, using 2 techniques: Injection and/or placement. Examples of through-the-needle injection techniques include intratumoral therapy, injection of alcohol and bupivacaine for celiac plexus neurolysis, and hydrogel for bleb formation to create space in the pancreaticoduodenal groove for dose-escalation stereotactic body radiation therapy. Examples of through-the-needle placement techniques include placement of fiducial markers, placement of ablative probes for non-thermal and thermal therapies, placement of radioactive seeds for brachytherapy, and placement of a lumen-apposing metal stent to create a gastrojejunostomy in patients with gastric outlet obstruction. The vast majority of these techniques have shown comparable or superior outcomes when compared to conventional interventions and therapies.

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INTRODUCTION

Pancreatic ductal adenocarcinoma has increased in incidence by 0.3% annually since 2006 and is expected to become the second cause of cancer-related death in the year 2030. It has the lowest 5-year relative survival of 11% compared to other solid organ malignancies, with an estimated death toll of 49830 which closely reflects its incidence of 62210 in 2021[1]. Approximately more than half of the patients presented at the metastatic stage, the highest proportion compared to other solid malignancies, while 13% and 29% presented at localized and regional stages, respectively. For those who present without overt evidence of metastasis, surgical resection is the ultimate goal to hopefully provide curative treatment. With the advancement of endoscopic ultrasound (EUS) in both diagnostic and therapeutic aspects of pancreatic cancer management, it has provided treatment options not only by tissue acquisition to get the definitive diagnosis of pancreatic cancer but also by more accurate local disease control in regional or locally advanced stages while awaiting definitive curative surgical resection and through palliative treatments in those with metastasis or advanced disease[2,3]. This review does not include EUS-guided intervention for malignant biliary obstruction.

EUS GUIDED TISSUE ACQUISITION

An initial randomized trial comparing the 22-gauge aspiration and 22-gauge biopsy needles for EUS-guided sampling of solid pancreatic mass lesions showed comparable diagnostic efficacy, technical performance, and safety profile without a significant difference in yield or quality of the histologic core between the two needle types[4]. Subsequent randomized trials with larger sample sizes were able to demonstrate that fewer passes were required to establish a diagnosis of pancreatic malignancy with improved histopathological quality using a fine needle biopsy (FNB) needle[5-7]. The use of the 25 gauge FNB needle was technically feasible, safe, efficient and was comparable to the standard 22 gauge fine needle aspiration (FNA) needle in patients with solid pancreatic masses in the absence of an on-site cytopathologist. The cytological sample quality in the liquid-based preparation and the histological diagnostic yield for specific tumor discrimination of EUS-guided sampling using a 25 gauge FNB needle were significantly higher than those using a 22 gauge FNA needle[8]. In terms of designs of FNB needle, an opposing bevel design provided significantly superior tissue yield and diagnostic performance when compared to a reverse bevel needle[9]. For second generation FNB needles, the diagnostic yield when used primarily without rapid on-site evaluation, was higher when a fork-tip needle, in comparison to a Franseen needle or FNA needle, was used[10,11]. However, a subsequent larger trial revealed that samples with the highest degree of cellularity in a single biopsy, resulting in a diagnostic accuracy of 90% or higher, were collected by FNB needles using the Franseen or fork-tip needle[12]. Another study showed that a 22-gauge Franseen needle provided more tissue for histologic evaluation and better diagnostic accuracy than a 20-gauge lateral bevel needle. These studies led to the technical guideline from the European Society of Gastrointestinal Endoscopy in 2017 suggesting performance of 3-4 needle passes with an FNA needle or 2-3 passes with an FNB needle when on-site cytologic evaluation is unavailable[13]. There may be some theoretical concern that the high yield of FNB needles might come with the cost of possibly higher risk of tract seeding, especially in patients with a resectable solid pancreatic mass, unless the tract itself is planned to be resected[14]. In terms of technique, the stylet slow pullback technique might enable better acquisition of tissue and increased cellularity for the diagnosis of pancreatic tumors suspected to be malignant, compared to the conventional negative suction after stylet removal technique or the non-suction after stylet removal technique, in the absence

of an on-site cytopathologist.

In the era of personalized medicine, next-generation sequencing (NGS) can serve as a complementary diagnostic test and unveil potentially predictive genomic biomarkers for treatment response[15,16]. An initial experience revealed that NGS can be performed on EUS-FNA-derived samples to provide information on *KRAS* mutation status and 160 other cancer genes such as *TP53*, *SMAD4*, *KMT2D*, *NOTCH2*, *MSH2*, *RB1*, *SMARCA4*, *PPP2R1A*, *PIK3R1*, *SCL7A8*, *ATM* and *FANCD2*, to supplement cytological evaluation[17-21]. Similar to the efficacy of FNB over FNA for cellularity, FNB should be considered when tumor genotyping is requested, as it was associated with a higher yield of sufficient sampling for genomic testing, especially in tumors of 3 cm or smaller, and tumors located in the head/neck of the pancreas[22]. Moreover, recent data indicated that studying the expression of a selected gene set could inform the selection of the most appropriate treatment for patients, moving towards an individualized medicine approach. To accomplish this, adequate EUS tissue acquisition will allow providers to build organoids platform that can allow determination of the transcription level of informative genes[23]. Early studies were able to demonstrate the successful isolation of organoids using samples obtained from a 22-gauge FNB needle at the time of the initial diagnosis, which may be helpful in patients with pancreatic cancer that are not surgically resectable[24,25].

EUS GUIDED PLACEMENT OF FIDUCIAL MARKERS

For patients with borderline resectable or locally advanced pancreatic cancer, neoadjuvant chemoradiation plays a vital role. While chemotherapy can potentially control systemic disease, local disease control by radiation therapy has shown additional benefit to hopefully reduce local recurrence after surgical resection[26,27]. Stereotactic body radiation therapy (SBRT) and image guided radiation therapy (IGRT) have increasingly been used in clinical practice since they can provide a higher dose of radiation with a shorter duration of treatment and acceptable rates of toxicity[28]. To be able to focally deliver radiation to the pancreas, which is an organ that moves following respiratory cycles, fiducial marker placement is recommended[29]. The markers are traditionally metallic, made of gold or platinum, or more recently, in hydrogel form, to serve as reference points for planning as well as follow-up daily image guidance over a short course of SBRT/IGRT. EUS-guided fiducial placement has evolved to become the technique of choice to place these fiducial markers, compared to conventional techniques where the markers are either placed surgically or percutaneously under cross-sectional imaging guidance such as computed tomography (CT) or transabdominal ultrasound[30]. The ideal characteristics of fiducial markers should have good visibility, minimal artifacts, and minimal migration over the course of SBRT/IGRT. Fiducials with larger diameters usually provide better visibility, at the cost of greater artifact. Furthermore, fiducial delivery systems that require a 19-gauge needle can pose challenges for EUS-guided fiducial placement when lesions are located at the pancreatic uncinate process. Therefore, the fine balance and preferred types of fiducials should be discussed in a multidisciplinary tumor board setting, especially between the endosonographers and the radiation oncologists. Generally, balanced visibility and artifacts can be achieved with a 0.35- to 0.43-mm diameter, 5- to 10- mm length, coiled or cylindrical gold fiducials[31]. A comparison study of these types of gold fiducials and the newer generations of fiducials, such as platinum or hydrogel, is still in process. A theoretical benefit of hydrogel compared to other metallic fiducials is that it can be injected *via* EUS in a liquid bleb formation to create additional space in the pancreaticoduodenal groove to separate the pancreatic head/neck cancer from the adjacent duodenal C loop (Figure 1) to allow for dose escalation during SBRT/IGRT while avoiding mucosal toxicity to the duodenum[32,33].

EUS-GUIDED INTRATUMORAL THERAPY

Given the close proximity of the probe of the therapeutic echoendoscope and several technologies that can be delivered through FNA needles, multiple modalities for local therapies of pancreatic cancer have been developed. These include placement of radiosensitive devices for brachytherapy, injections of antitumoral agents, access for passing through-the-needle probe for ablative devices, and photodynamic therapy.

EUS-GUIDED BRACHYTHERAPY

Intraoperative interstitial brachytherapy when used at laparotomy can improve local disease control in locally advanced pancreatic cancer. An initial animal study from China implementing EUS as a route for the implantation of radioactive seeds was proven safe and feasible. Shortly after, the group conducted a feasibility study in 15 patients who suffered from unresectable pancreatic cancer, showing 30% of patients had clinical benefit, with complications including pancreatitis and pancreatic fluid collection in

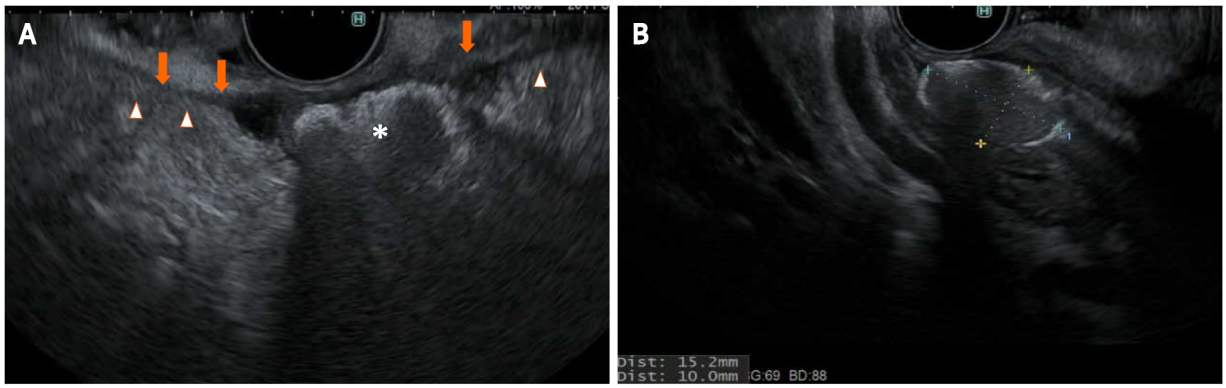

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Figure 1 Pancreaticoduodenal. A: A hydrogel bleb (asterisk) in the pancreaticoduodenal groove. The arrows demonstrate the line of the duodenum. The arrowheads demonstrate the line of the pancreas; B: The size of the hydrogel bleb, measured at 15.2 mm by 10 mm.

20% of patients. This was followed by a prospective cohort of 22 patients with unresectable pancreatic cancer who were treated with radioactive iodine 125 seeds, which resulted in 14% partial remission at 4 wk, 45% with stable disease, and 91% later succumbed to the disease at 2-year follow-up. Another group in China conducted a pilot study in 8 patients with T4 pancreatic cancer, using both intratumoral radioactive seeds and 5-fluorouracil, resulting in a 12% partial response at 3 mo, with overall 50% clinical benefits including a reduction in pain, without complications or hematologic toxicity[34]. Another prospective study showed that EUS-guided implantation of iodine-125 around the celiac ganglia can reduce pain visual analog scale score and analgesic drug consumption in patients with unresectable pancreatic cancer. A special EUS treatment planning system software may play a role in EUS-guided brachytherapy in patients with unresectable cancer, as it demonstrated a rate of partial remission of up to 80% in patients whose minimal peripheral dose was larger than 90 Gy, with a median survival time of 9 mo[35]. In addition to survival benefits, iodine-125 seed implantation placed percutaneously or *via* EUS after relief of obstructive jaundice *via* ERCP can improve biliary stent patency, time to development of gastric outlet obstruction, and improve quality of life by pain relief [36]. More recently, EUS guided placement of phosphorus-32 microparticles alone or with gemcitabine with or without nab-paclitaxel in unresectable locally advanced pancreatic cancer has been reported as alternative brachytherapy options[37,38]. The latter is an ongoing trial.

EUS-GUIDED INJECTION OF ANTITUMORAL AGENTS

Immunotherapy

The hypothesis of intratumoral therapy was based on that of other malignancies where both local disease control effect and systemic response effect (*i.e.*, metastasis) can be achieved through the immune response against the tumors, including breast cancer, renal cell carcinoma, and melanoma[39-43]. In addition, immunological responses induced by zoledronate-pulsed dendritic cell-based vaccines have been associated with therapeutic effects in clinical trials[44,45]. The first pilot study in patients with unresectable pancreatic cancer treated with EUS-guided injection of allogeneic mixed lymphocyte culture proved its feasibility and safety profile[46]. Subsequent pilot studies included an injection of immature dendritic cells in pancreatic cancer refractory to gemcitabine[47], a combination of systemic gemcitabine and intratumoral OK-432-pulsed dendritic cell therapy, followed by an intravenous infusion of lymphokine-activated killer cells stimulated with an anti-CD3 monoclonal antibody[48], and dendritic cell-based vaccination and concomitant chemotherapy in patients with advanced or recurrent pancreatic cancer[49]. The first phase 1 comparative trial of intratumoral injection of immature dendritic cells and OK-432 for resectable pancreatic cancer patients had one in nine patients with transient fever. Two out of nine patients treated with immunotherapy, one of whom had stage IV with distant lymph node metastasis, survived five years without further adjuvant therapy[50]. In a phase I/II trial of comprehensive immunotherapy combined with intratumoral injection of zoledronate-pulsed dendritic cells, intravenous adoptive activated T lymphocytes, and gemcitabine in unresectable locally advanced pancreatic cancer, a synergistic therapeutic response was shown with overall survival and progression-free survival of 12 and 5.5 mo, respectively[51]. To date, there has not been a study of EUS-guided intratumoral injection of other types of immunotherapy such as ipilimumab or nivolumab (Figure 2).

Chemotherapy

Pancreatic cancer is unfortunately insensitive to many chemotherapeutic drugs. It is thought that

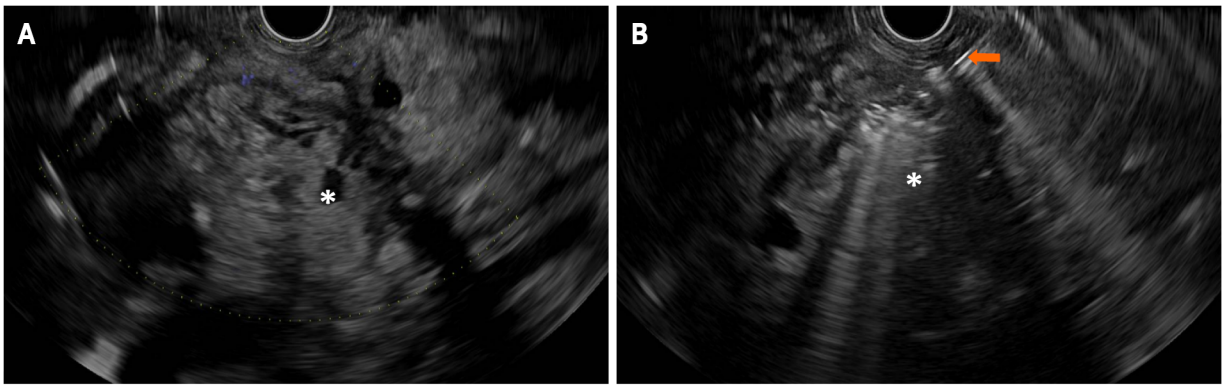

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Figure 2 Immunotherapy. A: An ill-defined heterogeneous mass of known pancreatic ductal adenocarcinoma (asterisk); B: Fine needle injection for intratumoral therapy. The arrows demonstrate a 19-gauge needle. The asterisk indicates the hyperechoic blush of the injectate.

inefficient delivery of chemotherapy into the tumor plays an important role in chemoresistance in pancreatic cancer. A combination therapy that can increase intratumoral vascular density and intramural concentration of gemcitabine was shown to lead to a transient stabilization of disease[52]. The initial experience using OncoGel (Regel/paclitaxel) for local tumor management *via* EUS guided 22-gauge needle in a pig model provided high and sustained localized concentrations of paclitaxel. A feasibility study using EUS-guided injection of gemcitabine in 38 patients with locally advanced and metastatic pancreatic cancer confirmed the safety and efficacy of the technique. More recently, a feasibility study of EUS guided injection of a novel polymer-based microparticles for a drug delivery system in a pig model appeared promising[53]. A phase I study evaluating the role of EUS guided injection of epidermal growth factor receptor antibody cetuximab as a radiosensitizer with chemoradiation for locally advanced pancreatic cancer in 16 patients proved its feasibility and safety profile when administered with abdominal radiation and concurrent gemcitabine. The incidence of grade 1-2 adverse events was 96% and the incidence of grade 3-4 adverse events was 9%[54].

Gene therapy

An initial feasibility study in 21 patients with locally advanced or metastatic pancreatic cancer treated with EUS guided injection of ONYX-015 (dl1520), an E1B-55kD gene-deleted replication-selective adenovirus that preferentially replicates in and kills malignant cells, was promising and generally well-tolerated either alone or in combination with gemcitabine[55]. In a multi-center feasibility study of 50 patients, intratumor delivery of TNFerade biologic (AdGVEFR.TNF.11D), a replication-deficient adenoviral vector that expresses tumor necrosis factor-alpha under the control of the Egr-1 promotor, by EUS-guided injection or percutaneously, combined with chemoradiation in the treatment of locally advanced pancreatic cancer, appeared promising, especially at the maximal tolerated doses. Adverse events such as cholangitis and pancreatitis were observed in 6%. The rate of patients who were able to proceed with surgery and achieve negative margin resection was 12%. In a randomized trial of 304 patients, treatment with TNFerade plus standard of care was safe but not effective for prolonging survival in patients with locally advanced pancreatic cancer[56].

For patients with unresectable pancreatic cancer, an open-label, dose-escalation trial using BC-819, which is a DNA plasmid developed to target the expression of diphtheria-toxin gene under the control of H19 regulatory sequences, in combination with systemic chemotherapy, may provide an additional therapeutic benefit, with minimal adverse events such as asymptomatic elevation of lipase[57]. EUS-guided injection of HF10, a spontaneously mutated oncolytic virus derived from herpes simplex virus 1 that has the potential to show a strong antitumor effect against malignancies without damaging normal tissue, in combination with erlotinib and gemcitabine, was a safe treatment for unresectable locally advanced pancreatic cancer[58]. The EUS-guided injection of STNM01, the double-stranded RNA oligonucleotide that specifically represses carbohydrate sulfotransferase-15, was safe and feasible without any adverse events. The authors also proposed that injections of STNM01 during the start of treatment could lower carbohydrate sulfotransferase-15 level, while its overexpression was associated with worse prognosis[59,60].

An open-label phase 1/2a study in the first-line setting of patients with inoperable locally advanced pancreatic cancer using an EUS guided injection of siG12D-LODER to release a siRNA drug against KRAS (G12D), along with systemic chemotherapy, was promising in terms of potential efficacy that 70% had a reduction in tumor marker CA 19-9, and 80% of patients had either stable disease or partial response with a median overall survival of 15 mo. However, one third of patients experienced serious adverse events.

EUS-GUIDED ABLATIVE THERAPIES

Radiofrequency ablation

Radiofrequency ablation is a local ablative method that can destroy the tumor by thermal coagulation and protein denaturation[61]. A phase II pilot study using radiofrequency ablation *via* a laparotomy in patients with locally advanced pancreatic cancer showed its feasibility and safety profiles with a 24% complication rate, with 9% requiring a reoperation. After a feasibility study in a porcine model, a feasibility study of using EUS-guided radiofrequency ablation of unresectable pancreatic cancer showed promising safety data, with one-third of the patients only developing mild abdominal pain without pancreatitis. The safety profile of the technique was later confirmed by subsequent feasibility studies showing no evidence of early or late major adverse events[62,63]. However, it required an 18-gauge electrode, which could be challenging for the treatment of lesions located in the pancreatic head or uncinate process. A new monopolar radiofrequency probe may be technically more versatile because it can be used through a 22-gauge needle[64]. In patients with locally advanced pancreatic cancer treated with EUS-guided radiofrequency ablation, those with wild-type SMAD4 may have improved survival benefits after treatment[65]. For other solid pancreatic lesions such as pancreatic neuroendocrine tumors and pancreatic insulinoma, EUS-guided radiofrequency ablation has shown clinical benefits such as fewer episodes of hypoglycemia[66,67], regression of neuroendocrine syndromes, improved pancreatic cystic sizes, and complete radiological ablation[64] A prospective study of 29 patients using EUS-guided radiofrequency ablation for pancreatic neuroendocrine tumors (PNET) and pancreatic cystic neoplasms revealed an overall tumor resolution of 86% in PNET and a significant response rate of 71% of patients with cystic neoplasms, with an overall complication rate of 10%.

Another application of radiofrequency ablation is to use it along with a simultaneous cryogenic cooling of carbon dioxide. An animal feasibility study was promising, given that only 14% of pigs developed histochemical pancreatitis after the procedure. The group has expanded this technique to 16 explanted pancreatic tumors from 16 patients, showing that the flexible bipolar ablation device, combining radiofrequency and cryotechnology, can create an ablation zone, defined by histological signs of coagulative necrosis, and that the extent of the ablation zone was related to the duration of application. However, data on this technique in in-vivo studies are still forthcoming.

Laser ablation

An initial animal study using a neodymium-doped:yttrium aluminum garnet (Nd:YAG) was based on the finding that the ablation resulted in a high rate of tissue necrosis and can be considered as a palliative option in patients with hepatocellular carcinoma, liver metastases in colorectal cancer, and malignant thyroid nodules[68-72]. There was no major post-procedural complication and all 8 pigs survived at 24 h after EUS-guided laser ablation of normal pancreatic tissue. The same group conducted another animal study to evaluate tissue temperature distribution, which plays a crucial role in the outcome laser-induced thermal therapy, proving that the tissue downward from the tip is mostly heated at 60 Celsius degree. The authors further conducted a human feasibility study in nine patients with unresectable pancreatic cancer who were unresponsive to previous chemoradiotherapy. Laser ablation was performed by using a 300-micrometer flexible fiber preloaded onto a 22-gauge fine needle. A 1064-nanometer wavelength Nd:YAG was used at different settings (2-4 Watts and 800-1200 Joules), resulting in an ablation area ranging from 0.4 cm^3 with the setting of 2 Watts and 800 Joules, to 6.4 cm^3 with the setting of 4 Watts and 1000 Joules, without adverse events. A comparative study using laser ablation compared to other EUS-guided techniques for patients with unresectable pancreatic cancer is awaiting.

Photodynamic therapy

EUS-guided photodynamic therapy has two steps: An injection of a photosensitizing agent, followed by the insertion of a 19-gauge needle into the targeted area to pass a small quartz optical fiber to illuminate and ablate tissue with the laser light. Initial pilot studies in porcine models using EUS-guided photodynamic therapy appeared promising. In a rabbit model, the efficacy of verteporfin delivery in tumors can be estimated by perfusion CT, to serve as a non-invasive method of mapping photosensitizer dose to enhance the outcomes of ablation with photodynamic therapy[73]. A human feasibility study in four patients with locally advanced pancreaticobiliary malignancies using a second-generation photosensitizer, a chlorin e6 derivative, and a flexible laser probe was promising, with a median volume of necrosis of up to 4 cm^3, no progression of disease over a median follow-up of five months, and no post-procedural complications. A prospective dose-escalation phase 1 study in 12 patients with treatment-naive locally advanced pancreatic cancer using intravenous porfimer sodium and illumination with a 630-nanometer light, followed by a CT scan to document change in pancreatic necrosis, and nab-paclitaxel and gemcitabine, showed an increased volume and percentage of tumor necrosis in 50% of patients after EUS-guided photodynamic therapy, without procedurally related adverse events. Another human feasibility study, which excluded patients with significant metastatic disease burden, disease involving > 50% duodenal or major artery circumference, and recent treatment with curative intent, investigated EUS-guided photodynamic therapy using a different photosensitizer, verteporfin, resulting in tissue necrosis in 62.5% of patients, with a mean diameter of 15.7 mm, and no

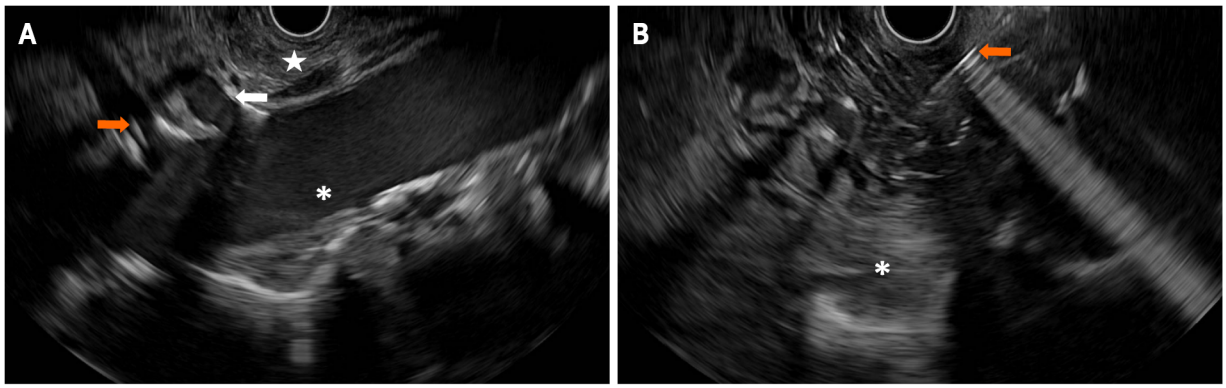

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Figure 3 Endoscopic ultrasound guided celiac plexus neurolysis. A: The structures while the echoendoscope is located at the posterior proximal gastric body/gastric cardia. A star demonstrates the pre-celiac region. The white arrow demonstrates the celiac trunk. A orange arrow demonstrates the superior mesenteric artery. An asterisk indicates the descending abdominal aorta; B: An area of hyperchoic blush of injected dehydrated alcohol (asterisk) delivered from a 19-gauge needle (arrow) for celiac plexus neurolysis.

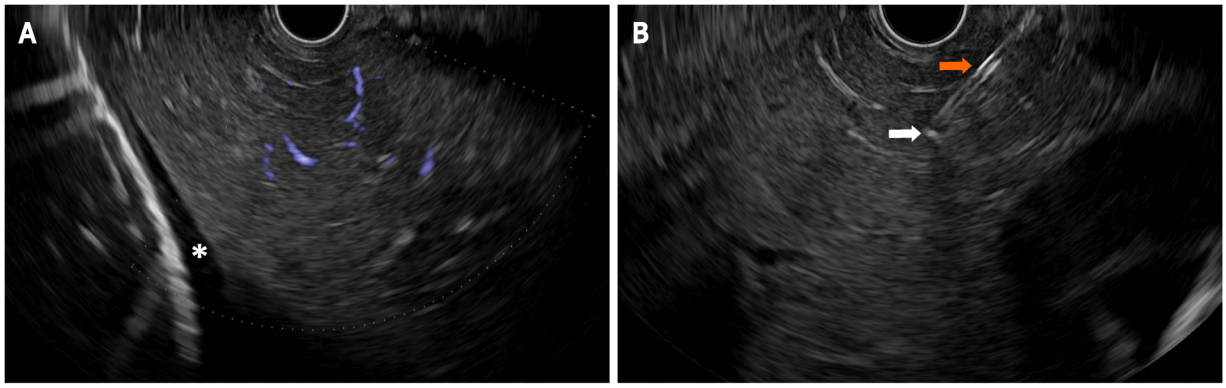

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Figure 4 Endoscopic ultrasound guided liver biopsy. A: Liver parenchyma without major intervening intrahepatic blood vessels, which is an optimal location for endoscopic ultrasound-guided liver biopsy. An asterisk indicates a small amount of perihepatic ascites; B: An endoscopic ultrasound-guided liver biopsy using a heparin-primed wet-suction technique *via* a 19-gauge Franseen needle tip design. The hyperechoic tip of the needle (white arrow) and the shaft of the needle (orange arrow) must be visualized at all times during the fine needle biopsy of the liver.

post-procedural related complications.

Alcohol

The vast majority of studies using EUS-guided ethanol ablation for solid pancreatic tumors are focused on non-functioning pancreatic neuroendocrine tumors and insulinoma[74-76]. Data of EUS-guided ethanol ablation in pancreatic ductal adenocarcinoma, especially in combination with EUS-guided celiac plexus neurolysis, are still needed.

EUS GUIDED CELIAC PLEXUS NEUROLYSIS

EUS-guided celiac plexus intervention has gained popularity in the management of pain from pancreatic cancer due to its safety profile when compared to narcotics[77]. An initial meta-analysis and systematic review showed that the pooled proportion of patients with pancreatic cancer treated with EUS-guided celiac plexus neurolysis had pain relief up to 53%-80% of the time[78-80]. The first randomized controlled trial in 96 patients assigned to either EUS-guided celiac plexus neurolysis or conventional pain management, showed that early EUS intervention reduced pain and may have moderated morphine consumption in patients with painful, inoperable pancreatic cancer, especially at 3 mo after treatment[81]. While the number of injections might not improve the degree of pain relief[82], the targeted celiac ganglia neurolysis was superior to celiac plexus neurolysis. EUS-guided radiofrequency ablation, using a 1 French monopolar probe passed through a 19-gauge targeting the area of celiac plexus or visualized ganglia, showed superiority in pain relief and improved quality of life when

compared to traditional EUS-guided celiac plexus neurolysis. However, a recent study raised the concern that combined celiac ganglion and plexus neurolysis may reduce median survival time without improving pain, quality of life, or adverse events when compared to traditional celiac plexus neurolysis. Furthermore, newer generations of opioids such as oxycodone and fentanyl may be comparable to EUS-guided celiac plexus neurolysis in terms of pain relief, quality of life, and opioid consumption (Figure 3).

EUS GUIDED GASTROENTEROSTOMY

Approximately 50% of patients with pancreatic cancer develop nausea and vomiting from malignant gastric outlet obstruction[83]. In patients with an inoperable stage, this was traditionally managed by endoscopic enteral stent placement or surgical gastrojejunostomy creation, depending on life expectancy. EUS-guided gastroenterostomy creation using a lumen apposing metal stent has emerged and gained in popularity due to a higher rate of initial clinical success and/or a lower rate of stent failure requiring repeat intervention when compared to enteral stent placement[84-86]. Compared to surgical approaches for gastrojejunostomy, EUS-guided gastroenterostomy was associated with fewer adverse events[87,88], shorter time to resume oral intake and chemotherapy, shorter lengths of stay, and reduced hospital costs. The technique of EUS-guided gastroenterostomy has been developed over time. The direct technique, defined by using an electrocautery-enhanced lumen-apposing metal stent, rather than a balloon-assisted approach, resulted in shorter procedure time and comparable clinical success (> 90%). In addition, the clinical success of direct-EUS-guided gastroenterostomy is durable with a low rate of re-intervention based on a long-term cohort[89]. Randomized trials comparing these endoscopic and surgical interventions for palliation of malignant gastric outlet obstruction caused by pancreatic cancer are awaiting. It should be noted that the learning curve of the technique can be challenging as it requires up to 40 procedures to achieve competency, otherwise fatal adverse events can occur at a very high rate (> 10%).

EUS GUIDED LIVER BIOPSY

Immune checkpoint inhibition targeted against cytotoxic T-lymphocyte-associated antigen 4 and programmed cell death protein 1 has shown survival benefit to treat multiple types of advanced cancer, including pancreatic cancer. Hepatotoxicity from checkpoint Inhibitors is a less common type of immune related adverse events, and it is often mild[90,91]. Concurrent treatment with nivolumab and ipilimumab, which is commonly used in pancreatic cancer, increases the risk of hepatotoxicity up to 37% and the risk of high-grade toxicity by up to 15%[92,93]. In complicated or severe forms, or unclear etiologies, liver biopsy can be used to confirm the etiology of injury[93,94], and/or to clarify the diagnosis in those with elevated liver enzymes refractory to steroid or immunosuppressant treatment [95].

EUS-guided liver biopsies have increased in popularity due to their decreased invasiveness compared to surgical routes and comparable tissue acquisition compared to transjugular or percutaneous route [96]. Bilobar liver biopsies, with one needle pass with three to-and-fro needle movements to each lobe of the liver, enhanced the assessment of disease severity due to an increased number of complete portal tracts, and longer aggregate specimen length, without severe adverse events[97]. A 19-guage Franseen-tip or reverse bevel core needle outperformed FNA needles or other types of core needles, resulting in longer aggregate length, more complete portal tracts, and more adequate specimens despite fewer passes. A heparinized wet suction technique can improve tissue adequacy compared with dry needle techniques. A randomized trial using these specific techniques for EUS-guided liver biopsies, compared to other conventional approaches, is needed (Figure 4)[98].

CONCLUSION

EUS-guided interventions provide a broad spectrum of treatment modalities for patients with borderline resectable, locally advanced, and inoperable pancreatic cancer. These include direct treatment for locoregional stages such as ablative therapies, brachytherapy, placement of fiducial markers for SBRT/IGRT, as well as palliative treatments such as EUS-guided gastroenterostomy creation for malignant gastric outlet obstruction and EUS-guided celiac plexus neurolysis to manage pain. While many of these procedures are considered investigational with limited data, particularly those from randomized controlled trials, the vast majority of these techniques have been widely used in clinical practice. For patient safety, it is important to note that most of these procedures should be performed at a facility with a multi-disciplinary tumor board and experienced interventional endosonographers.

FOOTNOTES

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MINIREVIEWS

Role of endoscopic ultrasound in esophageal cancer

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Abstract

Esophageal cancer (ECA) affects 1 in 125 men and 1 in 417 for women and accounts for 2.6% of all cancer related deaths in the United States. The associated survival rate depends on the stage of the cancer at the time of diagnosis, making adequate work up and staging imperative. The 5-year survival rate for localized disease is 46.4%, regional disease is 25.6%, and distant/metastatic disease is 5.2%. Additionally, treatment is stage-dependent, making staging all that much important. For nonmetastatic transmural tumors (T3) and/or those that have locoregional lymph node involvement (N), neoadjuvant therapy is recommended. Conversely, for those who have earlier tumors, upfront surgical resection is reasonable. While positron emission tomography/computed tomography and other cross sectional imaging modalities are exceptional for detecting distant disease, they are inaccurate in staging locoregional disease. Endoscopic ultrasound (EUS) has played a key role in the locoregional (T and N) staging of newly diagnosed ECA and has an evolving role in restaging after neoadjuvant therapy. There is even data to support that the use of EUS facilitates proper triaging of patients and may ultimately save money by avoiding unnecessary or futile treatment. This manuscript will review the current role of EUS on staging and restaging of ECA.

Key Words: Esophageal Cancer; Esophageal adenocarcinoma; Esophageal squamous cell carcinoma; Staging; Endoscopic ultrasound

Core Tip: Esophageal cancer (ECA) affects 1 in 125 men and 1 in 417 for women and accounts for 2.6% of all cancer related deaths. The associated survival rate depends on the stage of the cancer when it is first diagnosed; therefore, adequate work up and staging is imperative. Additionally, treatment is stage-dependent, making staging all that much important. Endoscopic ultrasound has played a key role in the locoregional staging of newly diagnosed ECA and has an evolving role in restaging after neoadjuvant therapy. This manuscript will review the current role of endoscopic ultrasound on staging and restaging of ECA.

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INTRODUCTION

The role of endoscopic ultrasound in esophageal cancer

There will be an estimated 19260 new cases of esophageal cancer (ECA) in the United States in 2021, which accounts for 1.0% of all new cancer cases. The lifetime risk for development of ECA in the United States is 1 in 125 for men and 1 in 417 for women[1]. Mortality from the disease is significant, with an estimated 15530 deaths in 2021, accounting for 2.6% of all cancer related deaths. When evaluating the data from 2011-2017, the 5-year survival rate was found to be 19.9%[2]. The associated survival rate depends on the stage of the cancer when it is first diagnosed. At the time of diagnosis, a significant subset of patients has either locally advanced or metastatic disease, with 34% of patients having regional spread and 39% of patients having distant or metastatic spread. Unfortunately, only 10% of patients present with localized disease. Five-year survival rates, as expected, vary based on disease extent found on index evaluation. The 5-year survival rate for localized disease is 46.4%, regional disease is 25.6%, and distant/metastatic disease is 5.2%.

The workup for esophageal and esophagogastric junction cancers requires accurate staging as treatment protocols are stage dependent. Upper gastrointestinal endoscopy is essential for the initial evaluation of an esophageal mass. Endoscopy with biopsies is often sufficient to establish the diagnosis of ECA, but in the rare instances that biopsies are nondiagnostic, endoscopic ultrasound (EUS), with fine needle aspiration (FNA) of the esophageal wall, can be utilized for tissue diagnosis[3]. Currently, ECA staging as defined by the American Joint Committee on Cancer staging system utilizes tumor-node-metastasis subclassifications, otherwise known as TNM. The TNM classifications refer to the primary tumor (T stage), regional lymph node status (N stage), and presence or absence of metastatic disease (M classification)[4]. After the initial diagnosis of cancer is made, the National Comprehensive Cancer Network recommends obtaining a computed tomography (CT) of the chest/abdomen/pelvis to assess for metastatic disease (this can also help to define local extent of disease and nodal involvement albeit not as well as EUS in most cases). If there is no overt evidence of M1 disease on cross sectional imaging, then both EUS and positron emission tomography (PET) are indicated at this time for further evaluation [5]. The primary strength of EUS as part of this algorithm is in the ability to establish the extent of locoregional involvement in patients without overt metastatic disease.

Since treatment options for ECA are stage dependent, EUS plays an important role by providing accurate T and N staging. Specifically, EUS helps differentiate patients that should undergo neoadjuvant chemotherapy from patients that would benefit from primary surgical resection.

Importance of esophagogastroduodenoscopy examination

In general, the endoscopic report during the workup for ECA should include several components, including the anatomic landmarks, location of the lesion in question, circumferential extent of the cancer, and the general mucosal appearance. The importance of accurately describing the location of the tumor cannot be overemphasized, as many of the cancers labeled as esophageal are in fact either junctional or primary cardiac/gastric. This distinction is primarily determined by where the bulk of the tumor is. The endoscopist needs carefully to examine and document if the cancer involves the cardia or crosses the junction and how long (in cm) it extends proximal to the esophagogastric junction. Additionally, it is important to look for "skip" lesions (submucosal proximal extension of the cancer) so that the surgeons are aware of the extent of the cancer proximally (Figure 1). Similarly, it is important to document if there is Barrett's esophagus that extends proximal to the cancer, since ideally this will also be resected if the patient is appropriate for surgery. Additionally, the most stenotic part of the tumor should be documented so that the endoscopist is aware and proceeds with appropriate caution when passing a larger diameter, often oblique viewing, echoendoscope.

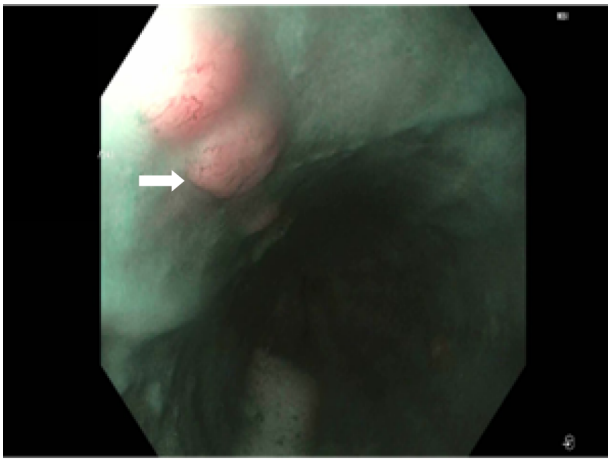

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Figure 1 Endoscopy revealing skip lesions, which represent submucosal spread of the cancer in the proximal esophagus.

EUS AND STAGING

T-Staging

Standard echoendoscopes operate at a frequency of 7.5-12 mHz. EUS can be performed using a radial or linear platform. Radial EUS images at a plane that is perpendicular to the long access of the scope, so the echo ultrasonographer can get a circumferential or 360 view of the ECA. These images are similar to interpreting axial CT slices (Figure 2A). Linear EUS, on the other hand, images parallel to the long access of the scope, and while T-staging is sometimes more challenging, use of this scope allows for performance of FNA or fine needle biopsy (FNB) if needed (Figure 2B). While choice of platform is typically operator dependent, it is common practice that endoscopists start with radial EUS because of the circumferential view. This can be switched to a linear EUS if something is found that needs FNA, such as a lymph node or liver lesion.

After identifying the distal and proximal extent of the cancer, the T-stage is determined. T staging refers to the depth of tumor invasion with respect to the extent of esophageal wall layer involvement. The esophageal wall is comprised of the mucosa, submucosa, muscularis propria, and adventitia. The mucosal wall layer is further subdivided into the epithelium, lamina propria, and muscularis mucosae. A basement membrane separates the muscularis mucosae from the submucosa. EUS helps to define the esophagus as a five layered structure with the first layer (hyperechoic) representing the superficial mucosa, the second (hypoechoic) representing the deep mucosa, the third (hyperechoic) representing the submucosa, the fourth (hypoechoic) the muscularis propria, and the fifth (hyperechoic) the adventitia (Figure 3). When reporting the T stage, the endosonographic report should also include the maximal wall thickness of the cancer.

EUS is particularly helpful with respect to T staging as we can accurately visualize and delineate the esophageal wall layers. Treatment decisions are partially dependent on T staging since depth of cancer penetration is important in predicting the risk of lymph node metastasis. Treatment for locally advanced disease, defined as stage IIB through IIIC, typically is neoadjuvant chemotherapy, with the goal to proceed with surgical resection following restaging, if appropriate. Neoadjuvant chemotherapy is associated with superior pathologic response and improved outcomes in these patients. For patients with surgically unresectable tumors or patients who are poor surgical candidates, definitive chemotherapy is offered.

T(is) refers to high grade dysplasia that is limited to the epithelium and does not penetrate the lamina propria. T1a tumors invade the lamina propria and/or muscularis mucosae, whereas T1b lesions invade into (but not through) the submucosa. By EUS, a T1a layer would invade through the first endosonographic, hyperechoic layer and possibly invade into, but not through the second hypoechoic later. T1b lesions would invade into, but not through the third, hyperechoic layer (Figure 4). T2 lesions invade past the submucosa into the muscularis propria (but do not breach the outer border). By EUS, these would invade into, but not through, the fourth (hypoechoic) layer. T3 lesions invade past the muscularis propria into the adventitia (Figure 5). By EUS, this would denote invasion past the fourth endosonographic layer into the fifth (hyperechoic) layer. T4a and T4b both invade structures adjacent to the esophagus, but T4a are considered resectable (invasion of pleura, pericardium, diaphragm), while T4b are considered unresectable (invasion of the aorta, vertebral body, trachea) (Figure 6). The true positive rate for EUS T-staging ranges between 0.89 (0.86-0.92), as gathered by one meta-analysis of 27 primary articles[6].

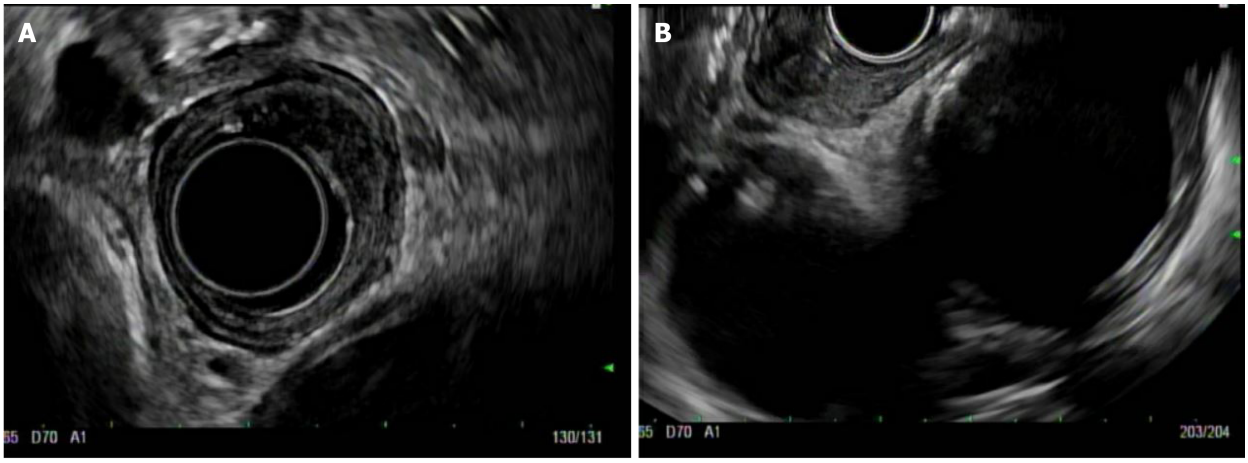

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Figure 2 Radial endoscopic ultrasound view of an early esophageal cancer (A) and linear endoscopic ultrasound view of the same lesion (B).

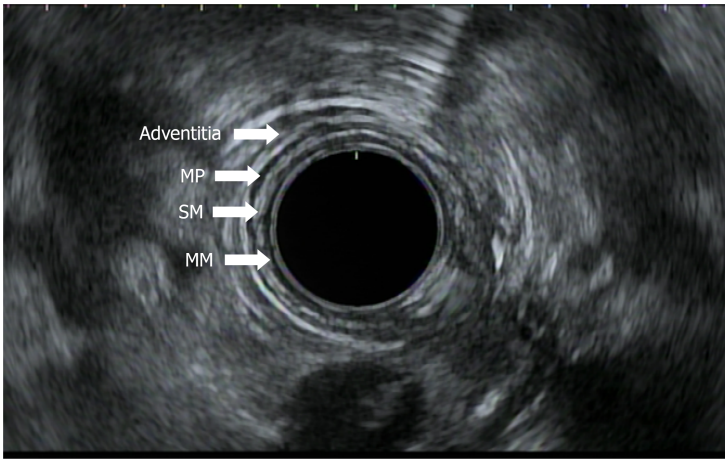

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Figure 3 Endoscopic ultrasound of normal esophageal wall layers. MM: Mucosa; SM: Submucosa; MP: Muscularis propria.

The accuracy of EUS lessens in staging cancers not on either ends of the spectrum (T1 or T/4). In a study by Tekola *et al*[7], 38 patients with ECA who were staged as T2N0 underwent surgery. EUS under staged 32% of these tumors. Other data have shown that up to 55% of tumors staged as T2N0 were shown to have nodal disease on resection. For this reason, many patients staged with T2N0 cancers are now undergoing preoperative chemoradiation. This practice is supported by Capovilla *et al*[11], whose study demonstrated that patients with T2N0 esophageal and squamous cell cancers who underwent neoadjuvant therapy had a statistically higher survival rate than patients who underwent up front surgery. If future studies support this practice, then the importance/ role of EUS in triaging patients to neoadjuvant *vs* surgery may in fact diminish[7-11].

"Importance of history/ presence of dysphagia in T staging": In patients with ECA who have dysphagia, the majority have advanced disease. One study showed that dysphagia was noted in 89% of patients having T3-4 ECA, while only 53% without dysphagia had T3-4 disease ($P < 0.001$). Another study showed similar findings where the presence of dysphagia in the setting of a cancer had a sensitivity 0.89 and sensitivity of 0.88 for at least locally advanced disease. For this reason, in patients with ECA and dysphagia, EUS may be less likely to affect treatment decisions[12,13].

N-staging

Next, the N-stage is determined. The N stage refers to the presence or absence, along with the total number of regional lymph nodes affected. N0 indicates the absence of lymph node involvement, N1 denotes two involved lymph nodes, N2, three to six involved lymph nodes, and N3, seven or more lymph nodes.

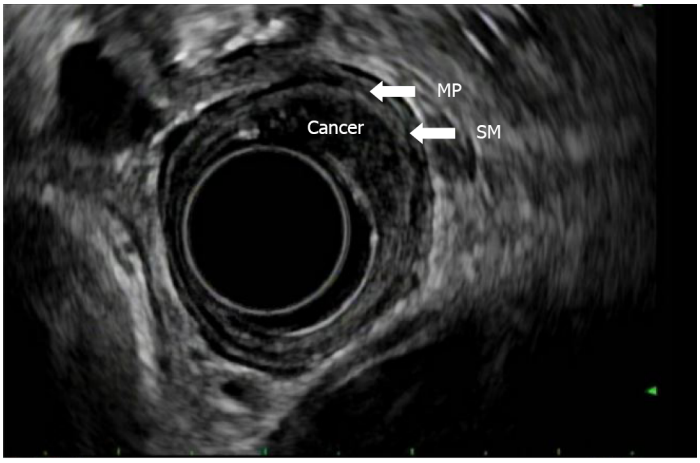

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Figure 4 Endoscopic ultrasound view of a T1b esophageal cancer. The cancer invades the submucosa but not the muscularis propria. SM: Submucosa; MP: Muscularis propria.

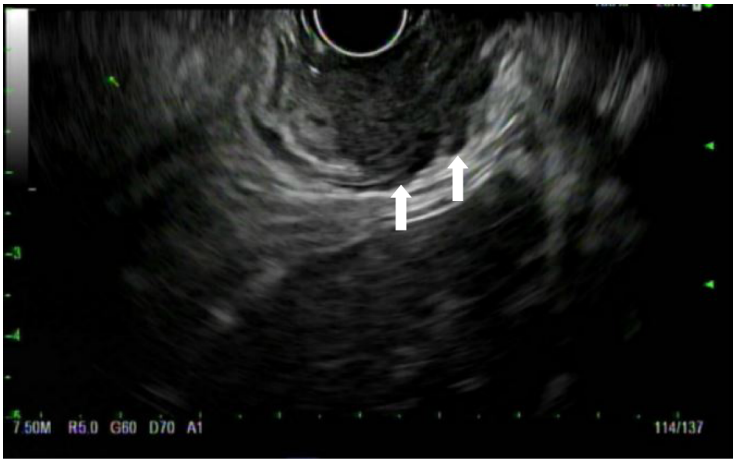

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Figure 5 Endoscopic ultrasound view of a T3 esophageal cancer. The cancer invades through the entire esophageal wall and invades the adventitia.

Endosonographic characteristics of lymph nodes that suggest malignant potential include size greater than 1 cm, round shape, sharp and demarcated borders, and hypoechoic echotexture (Figure 7). When a lymph node is found to possess all four of these aforementioned features, the accuracy of predicting a malignant lymph node is 80%-100%[14,15]. The location of the lymph node may also be informative in differentiation of benign and malignant. For example, the presence of celiac lymph nodes usually indicates pathology since they are not usually present. In one study, 89% of endosonographically detectable celiac lymph nodes were confirmed to be malignant on FNA[16]. Another predictor of malignant lymph node status includes association with T3-T4 staged lesions[17].

EUS has a pooled sensitivity of 59.5% to 97.2% sensitivity for N staging (40%-100% specificity). This is compared to a pooled sensitivity of 24% for distinguishing N0 from N1 by CT (with 100% specificity) [6]. Nodal staging is important prognostically since patients with nodal involvement have been found to have worse prognosis as compared to those who do not (N0 disease). Patients with 0, 1-2, and > 2 malignant appearing, peri-esophageal lymph nodes on index EUS were found to have 66 mo, 14.5 mo, and 6.5 mo, respectively, of median survival time[18].

M-staging

Lastly, distant lymph nodes, the liver, peritoneum, and the left adrenal gland are inspected for lesions. M staging differentiates presence of metastases (M1) *vs* absence of metastases (M0). As previously discussed, there is a limited role for EUS if M1 disease is established on CT. However, EUS at the position of the antrum or bulb of the duodenum can provide an important means for evaluation of peripancreatic or porta hepatis lymph nodes. In the body of the stomach, EUS can evaluate the liver (Figure 8), and in the fundus and cardia, EUS can evaluate perigastric and peripancreatic lymph nodes as well as evaluate the celiac plexus (though the latter is not considered M1). Additionally, EUS can

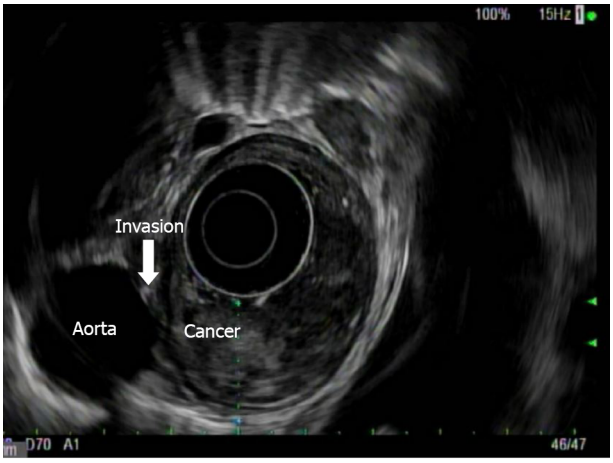

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Figure 6 Endoscopic ultrasound view of a T4 esophageal cancer. The cancer invades the aorta.

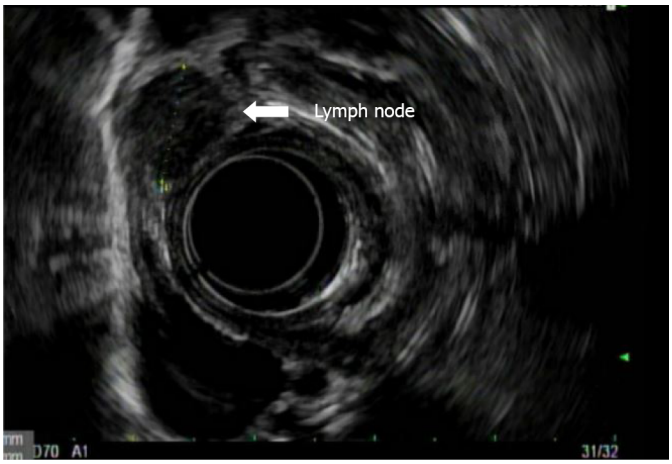

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Figure 7 Endoscopic ultrasound view of a malignant peritumor lymph node. It is hypoechoic, round, and greater than 1 cm in size and has distinct borders.

provide a detailed evaluation of the left adrenal gland and the peritoneum. An important difference between the older classification (American Joint Committee on Cancer) system and the current, affecting the utility of EUS in differentiating M0 from M1 disease, is that the involvement of a celiac lymph node is now considered regional (N) disease and no longer metastatic (M1a).

UTILITY OF EUS IN OBSTRUCTING TUMORS

EUS may not be technically feasible in patients with obstructing cancers. An obstructing tumor can be seen on presentation in up to 30% of cases. There are some risks of dilating a malignant stricture to pass an echo endoscope, including perforation[19]. Additionally, it may be difficult to stage accurately a lesion following esophageal dilation given disruption of normal tissue planes. There is questionable additional benefit of endosonography following the endoscopic finding of a malignant stricture as the presence of a malignant obstruction typically denotes advanced disease (T3-T4)[20]. Patients with malignant obstructions that cannot be traversed have poorer outcomes as compared to patients without evidence of stenosis, with median survivals of 10 mo *vs* 20 mo, respectively.

EUS-FNA

One of the benefits of EUS, specifically linear EUS, is the ability to perform FNA and/or FNB of lymph nodes and lesions in adjacent structures. EUS with FNA has 80% sensitivity in distinguishing T4 from T1-T3 disease and 78% accuracy in nodal staging[21]. In patients with T1-T2 disease, FNA can determine lymph node involvement, which in turn determines if these patients would theoretically need

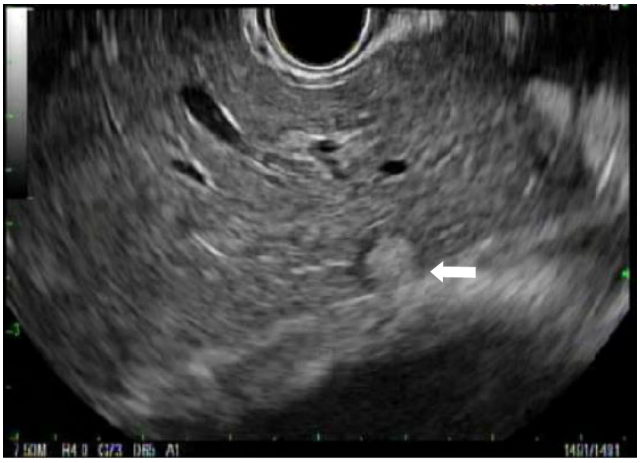

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Figure 8 Endoscopic ultrasound image of a round liver metastasis.

neoadjuvant chemotherapy or proceed directly to surgery. When performing FNA, it is important to avoid passing through the main tumor or major blood vessels to avoid both false positives as well as tumor seeding.

EUS vs other staging modalities

In one study, EUS results altered management by guiding the need for neoadjuvant chemotherapy in 34.8% of patients evaluated[22]. In another retrospective study of 56 patients, EUS was superior in the ability to identify locally advanced disease, with 58.9% sensitivity as compared to 26.8% and 37.5% sensitivity for CT and PET, respectively. EUS, however, is less accurate for early-stage lesions (T1 or T2) as compared with more advanced tumors. Additionally, PET is superior for detection of distant metastasis as compared to EUS, with a sensitivity of 81% *vs* 73% and specificity of 91% *vs* 86%, respectively[23]. EUS also plays an important role in detecting disease recurrence along with restaging after chemotherapy +/- radiation.

With improvements in imaging such as PET/magnetic resonance imaging (MRI), the overall utility of EUS is controversial. In one study of 74 patients undergoing preoperative staging, MRI outperformed EUS with higher specificity and accuracy in T staging[24]. In patients with dysphagia or an obstructing lesion, EUS has less utility given most of these patients have locally advanced disease and thus would not be definitive surgical resection candidates. In one study evaluating 147 patients with esophageal adenocarcinoma and dysphagia, 133 of these patients had a partially or completely obstructing mass on initial endoscopic evaluation. Overall, 128 of these 133 (96%) patients had locally advanced disease[12].

The utility of EUS is also diminished when evaluating early-stage ECA as there is loss of sensitivity for superficial disease. High frequency probes can help to provide better evaluation of the mucosa and the submucosa. In 75%-82% of cases, high frequency probes (12-20 MHz) can help distinguish T1a from T1b disease in patients without evidence of metastatic disease[25]. This can help determine candidacy for endoscopic resection techniques as a curative option during the same session. In another study, the accuracy of T staging when using a high frequency probe was 64% as compared to a conventional radial EUS, which was 49%[26]. When encountering a more superficial lesion that can be endoscopically resected, performing EUS first is helpful in confirming that the muscularis propria is uninvolved and in ruling out malignant lymphadenopathy. Once the lesion is endoscopically resected, then the true pathologic T stage is confirmed.

We have also found that EUS is challenging when evaluating early to intermediate gastroesophageal junction (GEJ) tumors. In one study evaluating EUS in GEJ tumors prior to surgical resection (in patients that had not undergone prior chemotherapy or radiation), EUS T staging was only accurate in 48% of cases (23% percent were under-staged and 29% were over-staged as correlated with pathologic T staging). This inaccuracy was even more pronounced in short segment tumors at the GEJ[27].

Role of EUS in restaging

The role of EUS in staging disease following neoadjuvant therapy is evolving. Patients are typically restaged after completion of neoadjuvant therapy to determine if the next most appropriate step is surgical resection *vs* definitive or palliative chemotherapy. Traditionally, it was thought that EUS is less reliable following neoadjuvant chemotherapy given inflammation and fibrosis sustained during treatment, which affects the ability to interpret reliably an EUS exam. The mucosal changes following neoadjuvant chemotherapy can cause hypoechoic appearance of the esophageal wall and over-staging of tumor invasion, possibly precluding some patients from an appropriate surgical resection. Following

neoadjuvant chemotherapy, a recent meta-analysis and systematic review found the sensitivity and specificity of T1 23% and 95%, T2 29% and 84%, T3 81% and 42%, and T4 43% and 96%, respectively. In the same study, the pooled sensitivity and specificity of N staging was found to be 69% and 52%, respectively[28].

Another retrospective study of 103 patients with locoregionally advanced ECA who had undergone neoadjuvant chemotherapy showed that reduced mass size, as determined by EUS (0.7 *vs* 1.7 cm, P = 0.01), correlated with a pathologic response[29]. However, in this same cohort, fluorodeoxyglucose-PET outperformed EUS in prediction of long-term survival following neoadjuvant chemotherapy (in patients following neoadjuvant chemotherapy but prior to surgical resection).

Even after surgery, EUS can be utilized in determining tumor recurrence, despite post-surgical EUS surveillance not being considered standard of practice at this time. In one small study of 40 patients who had undergone prior surgical resection, 3 recurrences were identified with EUS despite absence of symptoms (no reported dysphagia) and a negative CT[30]. In fact, another study of 43 patients undergoing q6 mo EUS surveillance had a 92% positive predictive value for early recurrence in a population where two-thirds of those with recurrence were asymptomatic[31].

In one meta-analysis, the pooled sensitivity for detecting complete pathologic response following neoadjuvant therapy was 0.35, 0.62, 0.01, and 0.08 for CT, PET-CT, EUS, and MRI, respectively. While the sensitivity of EUS was poor, specificity was 0.99 as compared to 0.83, 0.73, and 0.83 for CT, PET-CT, and MRI, respectively[32].

One multicenter study evaluating 138 patients before and after neoadjuvant therapy showed that EUS was able to detect adequately residual disease in 90% of patients 12 wk following therapy. Specifically, EUS was able to detect residual thickness and residual area of the tumor[33]. Another meta-analysis evaluating EUS for restaging following neoadjuvant chemotherapy found that EUS had a pooled sensitivity and specificity of 81% and 42% in T3 tumors (with markedly lower sensitivities of 23%, 29%, and 43% in T1, T2, and T4 tumors, respectively)[28].

EUS special considerations

Other considerations when discussing the role of EUS in the staging of ECA include the cost effectiveness. EUS performed prior to treatment decisions has been found to save $3443 per patient in its ability to identify stage 1 or stage 4 disease and avoid inappropriate neoadjuvant chemotherapy or surgery[34]. In patients without metastatic disease, EUS is the least expensive staging modality for ECA ($13811) as compared to CT-guided FNA ($14350) or surgery ($13992). While CT is the most appropriate initial staging test in most cases, EUS can theoretically suffice as a reasonable initial study as demonstrated in one single center study. EUS found advanced disease more frequently than CT (44 % *vs* 13%) and is cheaper ($804 *vs* $844) than CT (in cases where the probability of finding advanced disease is less than 20%)[35].

It is also important to note that performing high quality EUS is provider dependent and can vary with skill level and experience. In general, it is believed that at least 100 examinations are needed for a provider to provide T-staging reliably and accurately in ECA. High quality EUS examination also has been shown to improve survival in one randomized control trial of 223 patients with non-metastatic gastroesophageal cancer (hazard ratio of 0.706 with 95% confidence interval from 0.501 to 0.966)[36].

CONCLUSION

EUS has an important role in the staging of ECA. It is superior to cross sectional imaging in the locoregional staging of ECA. Unlike cross sectional imaging, it also has the added advantage to perform FNA and/or FNB of surrounding lymph nodes and organs and, consequently, alter management. Instances when EUS may not be as beneficial are in patients with dysphagia since they most likely have at least advanced locoregional disease and would undergo neoadjuvant or definitive therapy depending on their M status. While less accurate, EUS has an evolving role in neoadjuvant therapy. Since the performance of EUS is operator dependent, it should ideally be performed by physicians specifically trained in EUS.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Endoscopic retrograde cholangiopancreatography for bile duct stones in patients with a performance status score of 3 or 4

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Abstract

BACKGROUND

As the aging population grows worldwide, the rates of endoscopic retrograde cholangiopancreatography (ERCP) for common bile duct stones (CBDS) in older patients with a poor performance status (PS) have been increasing. However, the data on the safety and efficacy of ERCP for CBDS in patients with a PS score of 3 or 4 are lacking, with only a few studies having investigated this issue among patients with poor PS.

AIM

To examine the safety and efficacy of ERCP for CBDS in patients with a PS score of 3 or 4.

METHODS

This study utilized a retrospective multi-centered design of three institutions in Japan for 8 years to identify a total of 1343 patients with CBDS having native

papillae who underwent therapeutic ERCP. As a result, 1113 patients with a PS 0-2 and 230 patients with a PS 3-4 were included. One-to-one propensity-score matching was performed to compare the safety and efficacy of ERCP for CBDS between patients with a PS 0-2 and those with a PS 3-4.

RESULTS

The overall ERCP-related complication rates in all patients and propensity score-matched patients with a PS 0-2 and 3-4 were 9.0% (100/1113) and 7.0% (16/230; P = 0.37), and 4.6% (9/196) and 6.6% (13/196; P = 0.51), respectively. In the propensity score-matched patients, complications were significantly more severe in the group with a PS 3-4 than in the group with a PS 0-2 group (P = 0.042). Risk factors for complications were indications of ERCP and absence of antibiotics in the multivariate analysis. Therapeutic success rates, including complete CBDS removal and permanent biliary stent placement, in propensity score-matched patients with a PS 0-2 and 3-4 were 97.4% (191/196) and 97.4% (191/196), respectively (P = 1.0).

CONCLUSION

ERCP for CBDS can be effectively performed in patients with a PS 3 or 4. Nevertheless, the indication for ERCP in such patients should be carefully considered with prophylactic antibiotics.

Key Words: Endoscopic retrograde Cholangiopancreatography; Complication; Performance status; Risk factor

Core Tip: In 196 propensity-matched patients, the overall complications and technical success in patients with a performance status (PS) 3 or 4 were comparable to those of patients with a PS 0-2. However, complications were more severe in patients with a PS 3 or 4. In the multivariate analysis, indications of endoscopic retrograde cholangiopancreatography (ERCP) and the absence of antibiotics were significant risk factors for complications. Although ERCP for common bile duct stones can be effectively performed in patients with a PS 3 or 4, the indication for ERCP should be carefully considered, and prophylactic antibiotics should be administered to patients with a PS 3 or 4.

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INTRODUCTION

As the aging population grows worldwide, the rates of endoscopic retrograde cholangiopancreatography (ERCP) among the elderly are increasing. In particular, common bile duct stones (CBDS) are the most common indication for ERCP, and endoscopists often perform ERCP for CBDS in the elderly with poor Eastern Cooperative Oncology Group performance status (ECOG-PS) score[1], which is an objective index of activity in daily life, in clinical practice. Although several studies have reported that the safety and efficacy of ERCP for elderly patients aged ≥ 80-90 years were comparable to those in younger patients, the performance status (PS) score varied in the previous studies[2-10].

PS is an important tool utilized for the clinical determination of the indications and strategies of ERCP for CBDS in elderly patients. Evidence available from studies evaluating the safety and efficacy of ERCP for biliopancreatic diseases in patients with a poor PS score is limited[11,12]. Furthermore, few studies have investigated the safety and efficacy of ERCP for CBDS in patients with a poor PS score. In the present study, we assessed the safety and efficacy of ERCP for CBDS in patients with a PS score of 3 or 4 in comparison with those having a PS score of 0-2.

MATERIALS AND METHODS

Patients and study design

The data of patients with native major duodenal papilla who had undergone therapeutic ERCP for CBDS between April 2012 and February 2020 at Kumamoto Chuo Hospital, Saiseikai Kumamoto Hospital, and Kumamoto City Hospital in Japan were retrospectively reviewed. The exclusion criteria were (1) failure to detect CBDS during ERCP; (2) history of therapeutic ERCP; and (3) and a gastrointestinal tract that has already been surgically altered such as by employing Billroth II or Roux-en-Y reconstruction. The institutional review boards of the participating institutions approved this study and opt-out consent was applied. One-to-one propensity score matching analysis was performed to adjust for confounding factors between patients with a PS score of 0–2 and patients with a PS score of 3 or 4, and the safety and efficacy of ERCP for CBDS were compared between these two groups.

Outcomes and definitions

The primary outcome was the rates of post-ERCP complications and the rate of technical success such as complete stone removal and permanent biliary stent placement.

Post-ERCP complications included post-ERCP pancreatitis (PEP), bleeding, cholangitis, perforation, and aspiration pneumonia. These complications and their severity were diagnosed based on a lexicon for endoscopic complications[13]. When several complications were noted in the same patient, the most severe complication was selected for analysis.

Successful cases of complete stone removal or permanent biliary stent placement were considered a therapeutic success in this study.

Procedure

ERCP was performed in the prone or semi-prone position using side-viewing duodenoscopes (Olympus JF-260, TJF-260V; Olympus Medical Systems, Tokyo, Japan). Midazolam with pethidine hydrochloride was used for the purpose of sedation by the endoscopist. We determined the doses of midazolam and pethidine hydrochloride based on our sedation protocol using the data pertaining to the age and weight of patients. In patients aged 75-89 years and weighing < 70 kg, the dose of pethidine hydrochloride and midazolam was 17.5 mg-35 mg and 1 mg, respectively. In patients aged 75-89 years and weighing ≥ 70 kg, the dose of pethidine hydrochloride and midazolam was 17.5 mg-35 mg and 2 mg, respectively. In patients aged ≥ 90 years, the dose of pethidine hydrochloride and midazolam was 17.5 mg and/or 1 mg, respectively, regardless of the weight of the patients.

When a trainee with experience of < 200 ERCP procedures performed ERCP, an experienced endoscopist supervised them. After biliary cannulation using a standard ERCP catheter and a 0.025-inch guidewire, biliary stent placement or stone removal after endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD), or endoscopic papillary large balloon dilation (EPLBD) was performed. The treatment strategy for complete stone removal or permanent biliary stent placement was decided upon by the endoscopist.

Statistical analysis

Chi-squared test or Fisher's exact test was used for categorical variables, and Welch's *t*-test was used for continuous variables. A multivariate logistic regression model employed variables with *P* values < 0.20 in the univariate analyses to identify the predictive factors for post-ERCP complications.

One-to-one propensity score matching with a caliper of 0.2 was performed to adjust for confounding factors associated with post-ERCP complications between patients with a PS score of 0-2 and patients with a PS score of 3 or 4. Factors presented in Table 1 were used to construct propensity scores using the logistics regression model.

All statistical analyses were performed using EZR version 1.53 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria, version 4.1.0)[14]. Two-sided *P* values < 0.05 were considered statistically significant.

RESULTS

Patient characteristics

A total of 1343 patients met the inclusion criteria for this study. Altogether, 1113 and 230 patients were included in the groups with a PS score of 0-2 and 3-4, respectively. Details of patients' characteristics are presented in Table 1. Significant differences were noted in age, sex, indications of ERCP for CBDS, a history of cerebrovascular diseases, a history of multiple underlying diseases, antithrombotic treatment, non-dilated common bile duct (CBD), antibiotics, trainee involvement, difficult cannulation, EST, EPBD, EPLBD, use of balloon catheter, large stones, protease inhibitor, and rectal non-steroidal anti-inflammatory drugs. No significant differences were noted in patients' characteristics between the two groups

Table 1 Baseline characteristics of the patients

	All patients			Propensity score-matched patients		
	Patients with a PS 0-2 (*n* = 1113)	Patients with a PS 3 or 4 (*n* = 230)	*P* value	Patients with a PS 0-2 (*n* = 196)	Patients with a PS 3 or 4 (*n* = 196)	*P* value
Age [mean (SD)]	72.9 (14.0)	84.4 (9.1)	< 0.001	83.6 (8.2)	83.4 (9.2)	0.79
Female (%)	498 (44.7)	146 (63.5)	< 0.001	113 (57.7)	117 (59.7)	0.76
Indications of ERCP for CBDS						
Acute cholangitis (%)	607 (54.5)	194 (84.3)	< 0.001	160 (81.6)	160 (81.6)	1.0
Biliary pancreatitis (%)	59 (5.3)	5 (2.2)	0.041	5 (2.6)	5 (2.6)	1.0
Obstructive jaundice without cholangitis (%)	263 (23.6)	20 (8.7)	< 0.001	21 (10.7)	20 (10.2)	1.0
Asymptomatic CBDS (%)	184 (16.5)	11 (4.8)	< 0.001	10 (5.1)	11 (5.6)	1.0
Underlying diseases						
Diabetes Mellitus (%)	78 (7.0)	12 (5.2)	0.39	14 (7.1)	12 (6.1)	0.84
Cardiovascular diseases (%)	152 (13.7)	42 (18.3)	0.080	40 (20.4)	39 (19.9)	1.0
Cerebrovascular diseases (%)	55 (4.9)	53 (23.0)	< 0.001	31 (15.8)	31 (15.8)	1.0
Dialysis (%)	35 (3.1)	8 (3.5)	0.84	7 (3.6)	8 (4.1)	1.0
Liver cirrhosis (%)	15 (1.3)	0 (0.0)	0.089	0 (0)	0 (0)	1.0
Multiple underlying diseases (%)	99 (8.9)	37 (16.1)	0.002	33 (16.8)	30 (15.3)	0.78
Antithrombotic treatment	280 (25.2)	94 (40.9)	< 0.001	80 (40.8)	73 (37.2)	0.54
Billroth-1 reconstruction (%)	28 (2.5)	6 (2.6)	1.0	8 (4.1)	6 (3.1)	0.79
Post-cholecystectomy (%)	124 (11.1)	19 (8.3)	0.24	19 (9.7)	18 (9.2)	1.0
Presence of gallstones (%)	715 (64.2)	147 (63.9)	0.94	123 (62.8)	121 (61.7)	0.92
Normal serum bilirubin (%)	540 (48.5)	104 (45.2)	0.39	94 (48.0)	87 (44.4)	0.54
Platelet counts [mean (SD)] ($\times 10^6$/L)	19.1 (7.1)	19.5 (9.9)	0.44	18.7 (7.7)	18.6 (7.9)	0.93
PT-INR [mean (SD)]	1.2 (0.91)	1.2 (0.42)	0.29	1.3 (1.8)	1.2 (0.42)	0.47
Non-dilated CBD (< 10 mm) (%)	454 (40.8)	70 (30.4)	0.004	53 (27.0)	60 (30.6)	0.50
Periampullary diverticulum (%)	341 (30.6)	60 (26.1)	0.18	62 (31.6)	56 (28.6)	0.58
Antibiotics (%)	881 (79.2)	216 (93.9)	< 0.001	178 (90.8)	182 (92.9)	0.58
Trainees (%)	199 (17.9)	27 (11.7)	0.026	25 (12.8)	24 (12.2)	1.0
Successful biliary cannulation (%)	1099 (98.7)	225 (97.8)	0.35	192 (98.0)	192 (98.0)	1.0
Difficult biliary cannulation (%)	309 (27.8)	48 (20.9)	0.033	46 (23.5)	42 (21.4)	0.72
Contrast-assisted cannulation (%)	772 (69.4)	168 (73.0)	0.30	135 (68.9)	143 (73.0)	0.44
Wire-guided cannulation (%)	120 (10.8)	23 (10.0)	0.82	21 (10.7)	20 (10.2)	1.0
PGW-assisted cannulation (%)	156 (14.0)	30 (13.0)	0.75	28 (14.3)	26 (13.3)	0.88
Precut sphincterotomy (%)	63 (5.7)	9 (3.9)	0.34	12 (6.1)	7 (3.6)	0.35
Pancreatic injection (%)	513 (46.1)	93 (40.4)	0.13	87 (44.4)	81 (41.3)	0.61
EST (%)	973 (87.4)	186 (80.9)	0.011	154 (78.6)	160 (81.6)	0.53
EPBD (%)	125 (11.2)	38 (16.5)	0.034	38 (19.4)	31 (15.8)	0.43
EPLBD (%)	158 (14.2)	60 (26.1)	< 0.001	53 (27.0)	50 (25.5)	0.82

Use of balloon catheter (%)	896 (80.5)	167 (72.6)	0.010	139 (70.9)	144 (73.5)	0.65
Use of basket catheter (%)	504 (45.3)	105 (45.7)	0.94	102 (52.0)	94 (48.0)	0.48
Mechanical lithotripsy (%)	189 (17.0)	33 (14.3)	0.38	35 (17.9)	32 (16.3)	0.79
Biliary stent placement (%)	945 (84.9)	192 (83.5)	0.62	157 (80.1)	164 (83.7)	0.43
Number of CBD stones [mean (SD)]	2.2 (2.7)	2.5 (2.8)	0.052	2.6 (3.4)	2.6 (3.0)	0.87
Large stones (> 10 mm) (%)	195 (17.5)	61 (26.5)	0.002	57 (29.1)	52 (26.5)	0.65
Prophylactic pancreatic stent placement (%)	169 (15.2)	32 (13.9)	0.69	34 (17.3)	30 (15.3)	0.68
Protease inhibitor (%)	453 (40.7)	65 (28.3)	< 0.001	57 (29.1)	60 (30.6)	0.83
Rectal NSAIDs (%)	117 (10.5)	10 (4.3)	0.003	11 (5.6)	9 (4.6)	0.82

CBD: Common bile duct; CBDS: Common bile duct stones; ERCP: Endoscopic retrograde cholangiopancreatography; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; PS: Performance status; PGW: Pancreatic guidewire.

after propensity score matching.

Endoscopic retrograde cholangiopancreatography-related complications

ERCP-related complications in all patients and propensity score-matched patients are presented in Table 2. The overall ERCP-related complication rates in all patients and propensity score-matched patients in the groups with a PS score of 0-2 and 3-4 were 9.0% (100/1113) and 7.0% (16/230; $P = 0.37$) and 4.6% (9/196) and 6.6% (13/196; $P = 0.51$), respectively. In all patients, complications were more severe in the group with a PS score of 3-4 than in the group with a PS score of 0-2 ($P = 0.063$), although this finding was not statistically significant. In the propensity score-matched patients, complications were significantly more severe in the group with a PS score of 3 or 4 than in the group with a PS score of 0-2 ($P = 0.042$). The incidence rate of each complication, including PEP, bleeding, cholangitis, perforation, and aspiration pneumonia, was not significantly different between the two groups in all patients and propensity score-matched patients. Among all patients, the severity of PEP was significantly higher in patients with a PS score of 3 or 4 than in those with a PS score of 0-2 ($P = 0.034$), and the severity of other complications was not significantly different between the two groups. Among the propensity score-matched patients, the severity of each complication was not significantly different between the two groups.

Therapeutic success rates of ERCP and mean procedure time

Therapeutic success rates of ERCP and mean procedure time are presented in Table 3. Therapeutic success rates, including successful complete stone removal and permanent biliary stent placement, in all patients and propensity score-matched patients were 98.5% (1096/1113) and 97.4% (224/230; $P = 0.26$) and 97.4% (191/196) and 97.4% (191/196; $P = 1.0$), respectively. The rates of successful complete stone removal in all patients and propensity score-matched patients between patients with a PS score of 0-2 and 3 or 4 were 1064/1113 (95.6%) and 200/230 (87.0%; $P < 0.001$) and 92.3% (181/196) and 87.8% (172/196; $P = 0.18$), respectively. The rates of successful permanent biliary stent placement in all patients and propensity score-matched patients between the group with a PS score of 0-2 and 3 or 4 were 2.9% (32/1113) and 10.4% (24/230; $P < 0.001$) and 5.1% (10/196) and 9.7% (19/196; $P = 0.12$), respectively. Mean procedure times were not significantly different in all patients and propensity score-matched patients between the two groups ($P = 0.42$ and $P = 0.77$, respectively).

Predictive factors for ERCP-related complications after ERCP for CBDS

The results of univariate and multivariate analyses for risk factors of ERCP-related complications for CBDS are presented in Table 4. In univariate analysis, there was a significant difference in indications of ERCP for CBDS, absence of antibiotics, prolonged procedure, difficult biliary cannulation, pancreatic injection, contrast-assisted cannulation, prophylactic pancreatic stent placement, normal serum bilirubin level, and pancreatic guidewire-assisted cannulation. In multivariate analysis, indications of ERCP for CBDS and absence of antibiotics were significant risk factors for ERCP-related complications.

DISCUSSION

Several studies reported that ERCP can be performed for biliopancreatic diseases even in elderly patients aged over 80 years[2-10]. However, PS is an important factor in deciding the therapeutic

Table 2 Comparison of endoscopic retrograde cholangiopancreatography-related complications between patients with a performance status score of 0-2 and 3-4

	All patients			Propensity score-matched patients		
	Patients with a PS 0-2 (*n* = 1113)	Patients with a PS 3 or 4 (*n* = 230)	*P* value	Patients with a PS 0-2 (*n* = 196)	Patients with a PS 3 or 4 (*n* = 196)	*P* value
Overall complications, *n* (%)	100 (9.0)	16 (7.0)	0.37	9 (4.6)	13 (6.6)	0.51
Severity of overall complications			0.063			0.042
Mild (%)	65 (65.0)	6 (37.5)		7 (77.8)	3 (23.1)	
Moderate (%)	29 (29.0)	8 (50.0)		2 (22.2)	8 (61.5)	
Severe (%)	6 (6.0)	2 (12.5)		0 (0.0)	2 (15.4)	
PEP (%)	50 (4.5)	5 (2.2)	0.14	3 (1.5)	2 (1.0)	1.0
Severity of PEP (%)			0.034			0.10
Mild (%)	34 (68.0)	3 (60.0)		3 (100.0)	0 (0.0)	
Moderate (%)	14 (28.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Severe (%)	2 (4.0)	2 (40.0)		0 (0.0)	2 (100.0)	
Bleeding (%)	18 (1.6)	4 (1.7)	0.78	1 (0.5)	4 (2.0)	0.37
Severity of bleeding (%)			0.12			0.40
Mild (%)	12 (66.7)	1 (25.0)		1 (100.0)	1 (25.0)	
Moderate (%)	3 (16.7)	3 (75.0)		0 (0.0)	3 (75.0)	
Severe (%)	3 (16.7)	0 (0.0)		0 (0.0)	0 (0.0)	
Cholangitis (%)	18 (1.6)	4 (1.7)	0.78	3 (1.5)	4 (2.0)	1.0
Severity of cholangitis (%)			0.077			0.49
Mild (%)	14 (77.8)	1 (25.0)		2 (66.7)	1 (25.0)	
Moderate (%)	4 (22.2)	3 (75.0)		1 (33.3)	3 (75.0)	
Perforation (%)	10 (0.9)	0 (0.0)	0.23	1 (0.5)	0 (0.0)	1.0
Severity of perforation (%)			1.0			NA
Mild (%)	4 (40.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Moderate (%)	5 (50.0)	0 (0.0)		1 (100.0)	0 (0.0)	
Severe (%)	1 (10.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Pneumonia (%)	4 (0.4)	3 (1.3)	0.10	1 (0.5)	3 (1.5)	0.62
Severity of aspiration pneumonia (%)			1.0			1.0
Mild (%)	1 (25.0)	1 (33.3)		1 (100.0)	1 (33.3)	
Moderate (%)	3 (75.0)	2 (66.7)		0 (0.0)	2 (66.7)	

PEP: Post-endoscopic retrograde cholangiopancreatography pancreatitis; PS: Performance status; NA: Not available.

strategy in elderly patients with CBDS. Although conservative therapy or therapeutic ERCP can be selected for CBDS in patients with a PS score of 3 or 4, therapeutic ERCP is better because ERCP can resolve CBD obstruction caused by CBDS if ERCP can be performed safely and effectively even in elderly patients with a PS score of 3 or 4.

Only a few studies are available on the association between poor PS and ERCP-related complications. Previous studies reported that the rate of overall ERCP-related complications was not different between patients with a PS score of 0-2 and 3 or 4 having biliopancreatic diseases[12,15] but the rates of aspiration pneumonia and heart failure were higher in patients with a PS score of 3 or 4 than in patients with a PS score of 0-2[12]. Another retrospective study reported that the risk of pulmonary and severe complications was high, although ERCP could be performed effectively in patients with a PS score of 4

Table 3 Comparison of outcomes of endoscopic retrograde cholangiopancreatography between patients with a performance status score of 0-2 and performance status 3-4

	All patients			Propensity score-matched patients		
	Patients with a PS 0-2 (*n* = 1113)	Patients with a PS 3 or 4 (*n* = 230)	*P* value	Patients with a PS 0-2 (*n* = 196)	Patients with a PS 3 or 4 (*n* = 196)	*P* value
Therapeutic success, *n* (%)	1096 (98.5)	224 (97.4)	0.26	191 (97.4)	191 (97.4)	1.0
Successful complete stone removal (%)	1064 (95.6)	200 (87.0)	< 0.001	181 (92.3)	172 (87.8)	0.18
Permanent biliary stent placement (%)	32 (2.9)	24 (10.4)	< 0.001	10 (5.1)	19 (9.7)	0.12
Mean procedure time, min (SD)	27.5 (15.7)	26.5 (15.9)	0.42	26.9 (15.7)	27.3 (16.6)	0.77

PS: Performance status.

[11]. These studies included not only patients with CBDS but also patients with various biliopancreatic diseases.

In this study, we examined the outcomes of ERCP in patients with CBDS, which is the most common indication for ERCP. The rates of therapeutic success, including complete stone removal and permanent biliary stent placement, were comparable between patients with a PS score of 0-2 and those with a PS score of 3 or 4. Although the rates of overall and each ERCP-related complication were not different between the two groups, complications were generally observed to be more severe in patients with a PS score of 3 or 4. Therefore, ERCP for CBDS can be performed effectively in patients with a PS score of 3 or 4. However, endoscopists should try their best to reduce the occurrence of ERCP-related complications because these complications can be more severe in patients with a PS score of 3 or 4.

In this study, indications of ERCP for CBDS and absence of antibiotics were significant risk factors for ERCP-related complications in the multivariate analysis. While the patients with acute cholangitis and biliary pancreatitis had a low risk for ERCP-related complications, those with obstructive jaundice without cholangitis and asymptomatic CBDS had a high risk for ERCP-related complications. Therefore, we emphasize that the indication of ERCP for CBDS should be carefully considered in patients with a PS score of 3 or 4. Although patients with acute cholangitis and biliary pancreatitis should be endoscopically treated, conservative treatment or follow-up strategy might be considered as an appropriate alternative in patients without acute cholangitis, especially those with asymptomatic CBDS. Regarding the use of antibiotics, the European Society of Gastrointestinal Endoscopy guidelines suggested the use of antibiotic prophylaxis in selected patients such as immunocompromised patients[16]. Antibiotic prophylaxis before ERCP to prevent ERCP-related cholangitis and aspiration pneumonia may be administered in patients with a PS score of 3 or 4 because such patients can be immunocompromised.

A previous study revealed that long procedure time was a significant risk factor for ERCP-related complications in patients with a PS score of 4[11]. Although not statistically significant, a prolonged ERCP procedure tended to increase ERCP-related complications in this study. Permanent biliary stent placement without CBDS removal is a therapeutic option to shorten the procedure time. However, a randomized control trial demonstrated that long-term biliary complications at a median follow-up duration of 20 mo were significantly higher in the permanent biliary stent placement group (complication rate: 36%) than in the complete CBDS removal group (complication rate: 14%)[17]. Another retrospective study at a median follow-up duration of 623 d showed similar results[18]. Therefore, complete CBDS removal should be considered at first, and permanent biliary stent placement can be an option in patients with a PS score of 3 or 4 for whom a short prognosis is predicted, who have an underlying disease that is severe, and who are expected to receive prolonged ERCP procedures such as for large and multiple CBDS.

Unlike the results of previous reports[11,12], the rates of aspiration pneumonia were not different between the two groups, and there were no cardiovascular complications in this study. Our sedation protocol using the data pertaining to the age and weight of patients may be attributed to a low incidence of aspiration pneumonia in patients with a PS score of 3 or 4 in this study. Furthermore, careful vital sign monitoring was performed during ERCP, particularly in patients with poor PS.

There are several limitations of this study. First, this was a retrospective study that included specialized centers in Japan. Second, although we balanced patients' characteristics using one-to-one propensity score matching, some unmeasured confounding factors may exist. Therefore, some selection bias may not be excluded. Third, long-term outcomes of ERCP were not examined in this study. Future multicenter studies including large patient cohorts from institutions with different ERCP experiences are warranted to confirm the safety and efficacy of ERCP for CBDS in patients with a PS score of 3 or 4.

Table 4 Predictive factors for endoscopic retrograde cholangiopancreatography (ERCP)-related complications after ERCP for common bile duct stones

	Univariate analysis			Multivariate analysis		
	With complications (*n* = 116)	Without complications (*n* = 1227)	*P* value	Odds ratio	95%CI	*P* value
Indications of ERCP for CBDS			< 0.001	1.1	1.05-1.2	< 0.001
Acute cholangitis (%)	44 (37.9)	757 (61.7)				
Biliary pancreatitis (%)	1 (0.9)	63 (5.1)				
Obstructive jaundice without cholangitis (%)	35 (30.2)	248 (20.2)				
Asymptomatic CBDS (%)	36 (31.0)	159 (13.0)				
Absence of antibiotics (%)	41 (35.3)	205 (16.7)	< 0.001	1.7	1.04-2.7	0.034
Mean procedure time, min [mean (SD)]	33.4 (17.3)	26.7 (15.5)	< 0.001	1.01	1.00-1.02	0.098
Difficult biliary cannulation (%)	50 (43.1)	307 (25.0)	< 0.001	1.3	0.74-2.3	0.36
Pancreatic injection (%)	69 (59.5)	537 (43.8)	0.001	1.4	0.85-2.1	0.20
Contrast-assisted cannulation (%)	68 (58.6)	872 (71.1)	0.008	0.90	0.47-1.7	0.74
Prophylactic pancreatic stent placement (%)	27 (23.3)	174 (14.2)	0.014	0.77	0.45-1.3	0.33
Normal serum bilirubin (%)	68 (58.6)	576 (46.9)	0.019	0.86	0.53-1.4	0.52
PGW-assisted cannulation (%)	24 (20.7)	162 (13.2)	0.034	1.0	0.77-1.3	0.98
Precut sphincterotomy (%)	11 (9.5)	61 (5.0)	0.050	0.96	0.76-1.2	0.76
Age [mean (SD)]	72.5 (14.8)	75.1 (13.9)	0.051	1.0	0.98-1.01	0.66
Non-dilated CBD (< 10 mm) (%)	55 (47.4)	469 (38.2)	0.058	1.3	0.82-1.9	0.30
Protease inhibitor (%)	51 (44.0)	467 (38.1)	0.23			
EPBD (%)	18 (15.5)	145 (11.8)	0.24			
Trainees (%)	24 (20.7)	202 (16.5)	0.24			
Use of basket catheter (%)	47 (40.5)	562 (45.8)	0.29			
EPLBD (%)	15 (12.9)	203 (16.5)	0.36			
Platelet counts [mean (SD)] ($\times 10^6$/L)	19.8 (9.8)	19.1 (7.4)	0.39			
EST (%)	97 (83.6)	1062 (86.6)	0.40			
Rectal NSAIDs (%)	8 (6.9)	119 (9.7)	0.41			
Biliary stent placement (%)	95 (81.9)	1042 (84.9)	0.42			
Number of CBD stones [mean (SD)]	2.1 (3.0)	2.2 (2.7)	0.52			
Post-cholecystectomy (%)	10 (8.6)	133 (10.8)	0.53			
Complete stone removal (%)	108 (93.1)	1156 (94.2)	0.54			
Mechanical lithotripsy (%)	21 (18.1)	201 (16.4)	0.60			
Use of balloon catheter (%)	94 (81.0)	969 (79.0)	0.72			
Wire-guided cannulation (%)	13 (11.2)	130 (10.6)	0.88			
Female (%)	55 (47.4)	589 (48.0)	0.92			
PT-INR [mean (SD)]	1.2 (0.90)	1.2 (0.85)	0.93			
Antithrombotic treatment	32 (27.6)	342 (27.9)	1.0			

Billroth-1 reconstruction (%)	3 (2.6)	31 (2.5)	1.0
Presence of gallstones (%)	75 (64.7)	787 (64.1)	1.0
Successful biliary cannulation (%)	115 (99.1)	1209 (98.5)	1.0
Large stones (> 10 mm) (%)	22 (19.0)	234 (19.1)	1.0

CBDS: Common bile duct stones; CBD: Common bile duct; ERCP: Endoscopic retrograde cholangiopancreatography; PT- EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; PGW: Pancreatic guidewire; NSAIDs: Nonsteroidal anti-inflammatory drugs; INR: Prothrombin time-international normalized ratio.

In conclusion, ERCP for CBDS in patients with a PS score of 3 or 4 can be performed effectively. Thus, endoscopists should not be reluctant to perform ERCP for CBDS in patients with a PS score 3 or 4. Nevertheless, the indication of ERCP for CBDS, particularly in patients with asymptomatic CBDS, requires careful consideration, and antibiotics should be used before ERCP in patients with a PS score of 3 or 4.

CONCLUSION

ERCP for CBDS in patients with a PS score of 3 or 4 can be performed effectively. Thus, endoscopists should not be reluctant to perform ERCP for CBDS in patients with a PS score 3 or 4. Nevertheless, the indication of ERCP for CBDS, particularly in patients with asymptomatic CBDS, requires careful consideration, and antibiotics should be used before ERCP in patients with a PS score of 3 or 4.

ARTICLE HIGHLIGHTS

Research background

In parallel with the growing aging population worldwide, endoscopic retrograde cholangiopancreatography (ERCP) is being increasingly used in the treatment of common bile duct stones (CBDS) in patients with a poor performance status (PS). Therefore, determining the safety and efficacy of ERCP for CBDS in patients with a PS score of 3 or 4 is essential.

Research motivation

PS is an important tool to elucidate the indications and strategies of ERCP for CBDS in elderly patients. However, few studies examined the safety and efficacy of ERCP for CBDS in patients with a poor PS.

Research objectives

To examine the safety and efficacy of ERCP for CBDS in patients with poor PS, which is defined as a PS score of 3 or 4.

Research methods

We reviewed the medical records of three institutions in Japan from April 2012 to February 2020. The exclusion criteria were (1) failure to detect CBDS during ERCP; (2) history of therapeutic ERCP; and (3) and an already surgically altered gastrointestinal tract including Billroth II or Roux-en-Y reconstruction. Finally, we identified 1343 patients with choledocholithiasis who met the inclusion criteria for the study, and 1113 and 230 patients had PS scores of 0-2 and 3 or 4, respectively. One-to-one propensity score matching was performed to compare the safety and efficacy of ERCP for CBDS between patients with PS scores of 0-2 and 3 or 4.

Research results

The overall ERCP-related complication rates in all patients with PS scores of 0-2 and 3 or 4 were 9.0% (100/1113) and 7.0% (16/230; $P = 0.37$), respectively. In the propensity score-matched group, the overall ERCP-related complication rates were 4.6% (9/196) and 6.6% (13/196; $P = 0.51$) among patients with PS scores of 0-2 and PS 3-4, respectively, and complications were significantly more severe in the group with a PS score of 3-4 than in the groups with a PS score of 0-2 ($P = 0.042$). In multivariate analysis, risk factors for ERCP-related complications were indication of ERCP and absence of antibiotics ($P < 0.001$ and $P = 0.034$, respectively). Particularly, absence of acute cholangitis including asymptomatic CBDS, was associated with increased risk of ERCP-related complications. Therapeutic success rates, including complete CBDS removal and permanent biliary stent placement, in propensity score-matched patients

with PS scores of 0-2 and 3 or 4 were 97.4% (191/196) and 97.4% (191/196), respectively (P = 1.0).

Research conclusions

ERCP for CBDS can be performed effectively in patients with a PS score of 3 or 4. The rates of ERCP-related complications were similar between the patients with PS scores of 0-2 and 3 or 4; however, their severity was higher in the group with a PS score of 3 or 4 than in the group with a PS score of 0-2. The indication of ERCP for CBDS, particularly in patients with asymptomatic CBDS, requires careful consideration, and antibiotics should be administrated before ERCP in patients with a PS score of 3 or 4.

Research perspectives

The retrospective study design that included specialized centers in Japan was an important limitation of this study. Future multicenter studies including large patient cohorts from institutions with different ERCP experiences are warranted to confirm our findings.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Improving sessile serrated adenoma detection rates with high definition colonoscopy: A retrospective study

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Abstract

BACKGROUND

Sessile serrated adenomas (SSAs) are important premalignant lesions that are difficult to detect during colonoscopy due to poor definition, concealment by mucous caps, and flat appearance. High definition (HD) colonoscopy may uniquely aid in the detection of these inconspicuous lesions compared to standard definition (SD) colonoscopes. In the absence of existing clinical guidelines to obligate the use of HD colonoscopy for colorectal cancer screening in average-risk patients, demonstrating the benefit of HD colonoscopy on SSA detection rate (SSADR) may help strengthen the evidence to recommend its use in all settings.

AIM

To evaluate the benefit of HD colonoscopy compared to SD colonoscopy on SSADR in average-risk patients undergoing screening colonoscopy.

METHODS

Data from screening colonoscopies for patients aged 50-76 years two years before and two years after the transition from SD colonoscopy to HD colonoscopy at our large, academic teaching center were collected. Patients with symptoms of colorectal disease, positive occult blood test, history of colon polyps, cancer, polyposis syndrome, inflammatory bowel disease or family history of colon cancer or polyps were excluded. Patients whose endoscopists did not perform colonoscopies both before and after scope definition change were also excluded. Differences in individual endoscopist SSADR, average SSADR, and overall SSADR with SD colonoscopy *vs* HD colonoscopy were also evaluated for significance.

RESULTS
A total of 3657 colonoscopies met eligibility criteria with 2012 colonoscopies from the SD colonoscopy period and 1645 colonoscopies from the HD colonoscopy period from a pool of 11 endoscopists. Statistically significant improvements of 2.30% in mean SSADR and 2.53% in overall SSADR were noted with HD colonoscopy (P = 0.00028 and P = 0.00849, respectively). On the individual level, three endoscopists experienced statistically significant benefit with HD colonoscopy (+5.74%, P = 0.0056; +4.50%, P = 0.0278; +4.84%, P = 0.03486).

CONCLUSION
Our study suggests that HD colonoscopy statistically significantly improves sessile serrated adenoma detection rate in the screening of average risk patients during screening colonoscopy. By improving the detection and removal of these lesions, adoption of HD colonoscopy may reduce the significant premalignant burden of sessile serrated adenomas.

Key Words: Colonoscopy; High definition; Standard definition; Sessile serrated adenoma; Colorectal cancer screening

Core Tip: Sessile serrated adenomas (SSA) have become increasingly recognized as important premalignant lesions that are difficult to detect during colonoscopy due to similarity in appearance to surrounding colonic mucosa. We performed a retrospective study to evaluate the impact of high definition (HD) colonoscopy compared to standard definition colonoscopy on SSA detection rate (SSADR) during screening colonoscopy. Our study found a statistically significant benefit to SSADR with HD colonoscopy that also met benchmark detection rates. To our knowledge, this study is the first to show the utility of HD colonoscopy for SSADR in average-risk patients, thereby demonstrating it as an important tool for routine colorectal cancer screening. In the absence of a strong clinical guideline to obligate the use of HD colonoscopy, the benefit demonstrated to SSADR by HD colonoscopy in our study may help strengthen the evidence to recommend its use in all settings.

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INTRODUCTION

Serrated adenomatous lesions have been increasingly recognized for their potential for transformation into malignancy more rapidly than conventional adenomas, contributing to approximately 15%-30% of all colorectal cancers (CRC). Serrated adenomas are typically classified into three types: sessile serrated polyps/adenomas (SSA), hyperplastic polyps (HP), and traditional serrated adenomas (TSA). Among these subtypes, SSAs are important due to their malignant potential and difficulty in detection during colonoscopy given poor circumscription, concealment by mucous caps, and flat appearance[1,2]. An analysis of two databases of screening colonoscopies in 2012 approximated that the prevalence of proximal serrated polyps (SSA, HP, and TSA) may be as high as 18%-20%[3]. Given the prevalence of SSAs, their difficulty in detection and their significant malignant potential, there is a critical need to improve the detection of this subtype of serrated lesions during screening colonoscopy[1].

Few endoscopic interventions have been found to meaningfully improve SSA detection rate (SSADR). Slower withdrawal time has shown efficacy according to a Dutch study that reported an OR of 1.12 (95%CI: 1.10-1.16) for proximal serrated polyp (SSA, HP, and TSA) detection with longer withdrawal times[4]. This is supported by data from the New Hampshire colonoscopy registry that demonstrated an increasing rate of serrated lesion detection (SSA and HP) per minute between 6-9 min of withdrawal time[4,5]. Similarly, chromoendoscopy with indigocarmine dye as surface contrast agent has also been suggested to enhance the detection of sessile lesions (SSA and HP) compared to conventional colonoscopy (1.19 *vs* 0.49 per patient, P < 0.001)[6]. Finally, use of the mucolytic agent acetic acid compared to normal saline during colonoscopy has been shown to significantly improve SSA detection in the right colon (13.5% *vs* 0.5%, P < 0.001)[7]. Interventions that have shown negligible improvement in SSADR include: narrowed spectrum endoscopy, antispasmodics, and wide angle and enhanced

mucosal views. High definition (HD) colonoscopy, on the other hand, has been cited as possibly beneficial in the detection of serrated polyps by the British Society of Gastroenterology, although data is lacking on its efficacy[1].

Though HD colonoscopy has been touted for its perceived benefits in the detection of adenomas due to heightened image resolution and magnification, there is still a lack of sufficient high quality data to obligate its use. The most recent position by the European Society of Gastrointestinal Endoscopy (ESGE) on the adoption of HD colonoscopy for overall adenoma detection in average risk patients is weak, citing inconsistent trial results, which may deter centers that currently use SD colonoscopy from adopting HD colonoscopy[8,9]. Given the lack of data on the adoption rate of HD colonoscopy outside of tertiary care centers, proving the benefit of HD colonoscopy on the detection of premalignant SSAs, specifically, may help strengthen the evidence behind its use in all settings.

Given the limited high-quality data supporting the use of HD colonoscopy in screening average-risk populations, it is understandable that there is also minimal data specifically on the impact of HD colonoscopy and SSADR. A recent study by Roelandt *et al*[10] that compared effects of endoscopy system, colonoscope definition, and virtual chromoendoscopy performed a subgroup SSADR analysis found significant benefit with 582 HD colonoscopies compared to 505 SD colonoscopies (8.2% *vs* 3.8%, respectively). However, a significant limitation of this study, was its inclusion of diagnostic (32.1%) as well as surveillance colonoscopies (29.3%), likely performed to increase sample size but potentially misrepresenting the improvement in SSADR that can be attributed to HD colonoscopy[10,11]. Another study by East *et al*[12] of 72 standard colonoscopies and 58 HD colonoscopies that investigated improvements in hyperplastic polyp detection (defined to include SSA and HP) with optimized withdrawal technique found a nonsignificant improvement with HD colonoscopy. It should be noted, however, that given the small study size, the benefit to SSADR may not be detectable especially given that SSAs make up a relatively lower proportion of all polyps detected on colonoscopy[12].

Based on the limited high powered, high quality studies available on detection of SSAs in HD colonoscopy, there is room in the literature for additional study on this subject. As such, we performed a retrospective study to evaluate the impact of HD colonoscopy compared to SD colonoscopy on SSADR exclusively during screening colonoscopy. Our secondary analysis compared overall adenoma detection rates with HD colonoscopy *vs* SD colonoscopy at our center.

MATERIALS AND METHODS

Materials

All colonoscopies performed at our tertiary medical center in the two years before and after the transition from SD colonoscopy to HD colonoscopy on June 2nd, 2018 were identified. All other procedural elements were uniform during the 4-year study period. All pathology specimens were reviewed solely by the pathology department at our institution. For the primary SSADR analysis, each colonoscopy report and associated pathology report during the defined study period were collected, from which patient demographics, colonoscopy date, colonoscopy indication, colonoscopy findings (polyp/lesion presence and type), and endoscopist data were compiled. For the secondary analysis involving adenoma detection rate (ADR), preexisting ADR data from our center with the same inclusion criteria during the same time period was used.

Inclusion criteria

All patients aged 50-76 years who underwent a screening colonoscopy between June 1, 2016 – June 2, 2020 were included. Patients with any symptoms of colorectal disease, positive occult blood test, history of colon polyps, cancer, polyposis syndrome, inflammatory bowel disease or family history of colon cancer or polyps were excluded. Patients whose endoscopists did not perform colonoscopies both before and after scope definition change were also excluded.

Statistical analysis

All statistical analyses were performed with Microsoft Excel and JMP PRO 15 software. Two-sided *P*-values < 0.05 were considered significant. Biostatistical analysis was performed by the authors.

The average age and the sex distribution of the SD colonoscopy group (June 1, 2016 – June 1, 2018) and the HD colonoscopy group (June 2, 2018 – June 2, 2020) were compared for demographic data. These comparisons were only performed with data from the SSADR analysis.

The primary outcome measure was SSA detection rate (SSADR), defined as the proportion of eligible colonoscopies in which at least one SSA was identified, for both the SD and HD colonoscopy periods. Individual differences in endoscopist SSADRs with SD colonoscopy and HD colonoscopy were evaluated by Z-test. Mean SSADR and overall SSADR were also reported. Mean SSADRs were calculated as the average of the individual endoscopist SSADRs. The difference in mean SSADRs with SD and HD colonoscopy was evaluated with the paired *t*-test. Overall SSADRs were calculated as the sum of all SSA-positive colonoscopies over the total number of eligible colonoscopies. The difference in overall SSADR with SD and HD colonoscopy was evaluated with the Z-test.

Table 1 Demographic characteristics of the standard definition colonoscopy and high definition colonoscopy groups

Variable	Standard definition, *n* = 2012	High definition, *n* = 1645	*P* value
Age (yr), mean (range)	59.3 (50-76)	59.2 (50-76)	0.985
Gender, male (%)	896 (44.5%)	757 (46.0%)	0.36812

Table 2 Endoscopist, overall, and average sessile serrated adenomas detection rates with corresponding colonoscopy volumes during standard definition colonoscopy and high definition colonoscopy

Endoscopist	Standard definition		High definition		Δ	*P* value (α < 0.05)
	Eligible colonoscopies	SSADR	Eligible colonoscopies	SSADR		
1	166	4.22%	229	2.18%	-2.03%	0.24604
2	303	2.97%	279	4.66%	1.69%	0.28462
3	82	0.00%	124	2.42%	2.42%	0.1556
4	171	5.26%	37	5.41%	0.14%	0.9681
5	63	0.00%	51	3.92%	3.92%	0.11184
6	135	1.48%	98	4.08%	2.60%	0.21498
7	125	1.60%	76	2.63%	1.03%	0.61006
8	410	6.34%	356	12.08%	5.74%	0.0056
9	238	1.68%	97	6.19%	4.50%	0.0278
10	191	2.62%	161	7.45%	4.84%	0.03486
11	128	3.91%	137	4.38%	0.47%	0.8493
Overall	2012	3.43%	1645	5.96%	2.53%	0.00028
Average	182.91	2.73%	149.54	5.04%	2.30%	0.00849

SSADR: Sessile serrated adenomas detection rate.

A secondary outcome measure was ADR, defined as the proportion of eligible colonoscopies in which at least one adenoma of any type was identified. Individual differences in endoscopist ADRs with SD and HD colonoscopy were evaluated with the Z-test. Mean ADR and overall ADR were also reported. Mean ADRs were calculated as the average of the individual endoscopist ADRs. The difference in mean ADRs with SD and HD colonoscopy was evaluated with the paired *t*-test. Overall ADRs were calculated as the sum of all SSA-positive colonoscopies over the total number of eligible colonoscopies. The difference in overall ADR with SD and HD colonoscopy was evaluated with the Z-test.

RESULTS

Following review of the data, 3657 cases met eligibility criteria with 2012 colonoscopies in the SD group and 1645 colonoscopies in the HD group for the SSADR analysis. Eleven endoscopists performed colonoscopies both before and after implementation of HD colonoscopy on June 2, 2018.

Demographic analysis of the SD and HD groups (Table 1) show the average age in both groups was 59 years and that males comprised approximately 45% of both groups. There was no significant difference in average age or sex distribution between the SD and HD groups.

The mean SSADRs with SD colonoscopy and HD colonoscopy were 2.73% and 5.04%, respectively, yielding a statistically significant improvement of 2.30% (P = 0.00028). Comparison of the overall SSADRs also showed a statistically significant improvement from 3.43% with SD colonoscopy to 5.96% with HD colonoscopy (Δ 2.53%, P = 0.00849). Most of the endoscopists also demonstrated individual increases in SSADR with HD colonoscopy. On the individual level, three endoscopists experienced statistically significant benefit with HD colonoscopy (+5.74%, P = 0.0056, +4.50%, P = 0.0278, +4.84%, P = 0.03486). One endoscopist had a reduction in SSADR, but this difference was statistically nonsignificant (-2.03%, P = 0.24604) (Table 2 and Figure 1A).

Table 3 Endoscopist, overall, and average adenoma detection rates with corresponding colonoscopy volumes during standard definition colonoscopy and high definition colonoscopy

Endoscopist	Standard definition		High definition		Δ	*P* value (α < 0.05)
	Eligible colonoscopies	ADR	Eligible colonoscopies	ADR		
1	262	30.15%	250	28.80%	-1.35%	0.72786
2	492	25.20%	311	44.37%	19.17%	< 0.00001
3	49	6.12%	104	38.46%	32.34%	< 0.00001
6	145	31.72%	104	39.42%	7.70%	0.20766
7	245	21.22%	127	31.50%	10.27%	0.02926
8	493	31.64%	360	43.61%	11.97%	0.00034
9	283	29.68%	78	32.05%	2.37%	0.68916
10	289	24.91%	162	38.27%	13.36%	0.00288
11	91	42.86%	138	43.48%	0.62%	0.92828
Overall	2349	27.88%	1634	38.86%	10.98%	< 0.00001
Average	261	27.06%	181.6	37.77%	10.72%	0.01522

ADR: Adenoma detection rate.

Preexisting ADR data was only available for nine of the eleven endoscopists. The mean ADRs with SD colonoscopy and HD colonoscopy were 27.06% and 37.77%, respectively, yielding a significant improvement of 10.72% (P = 0.01522). Comparison of the overall ADRs also showed a significant improvement with HD colonoscopy (Δ 10.98%, P < 0.00001). Most of the endoscopists demonstrated individual increases in ADR with HD colonoscopy. Five of these endoscopists saw significant benefit. One endoscopist had a minimal reduction in ADR, but this difference was nonsignificant (Table 3 and Figure 1B).

DISCUSSION

Identifying techniques that improve the detection of SSAs will help reduce interval colon cancer in screening colonoscopy[1,3]. In the absence of high-quality evidence to obligate the use of HD colonoscopy for the average-risk population, we performed a retrospective study to evaluate the benefit of HD colonoscopy compared to SD colonoscopy on SSADR during screening colonoscopy[8]. In addition to the significant improvements to both average and overall SSADRs, benefit from HD colonoscopy was further underscored by the average SSADR surpassing the serrated lesion benchmark detection rate of 7% (inclusive of HPs)[1,11]. To our knowledge, this study is the first to illustrate the utility of HD colonoscopy for SSADR in average risk patients, solidifying its role as a tool in high quality CRC screening.

Notably, our study demonstrated significant benefit to all adenoma/polyp detection rates, not simply SSADR. It should be acknowledged, however, that it is possible that our ADR outcomes were improved slightly by the independent improvement of endoscopists during the four-year study period or by HD colonoscopy itself. Interestingly, our data is also consistent with an existing study by Waldmann *et al*[13] that reported significant increases in ADR with HD colonoscopy in endoscopists with historically lower ADR , as each of the four endoscopists in our study with an ADR < 30% experienced statistically significant increases in ADR with HD colonoscopy. In contrast, four of the five endoscopists with an ADR ≥ 30% with SD colonoscopy did not experience such improvement with HD colonoscopy in our study, further supporting the selective benefit of HD colonoscopy for endoscopists with lower ADRs.

A major strength to our study is the exclusion of surveillance and diagnostic procedures to focus solely on screening colonoscopies. This is in contrast to the existing study by Roelandt *et al*[10] on HD colonoscopy and SSADR that included both diagnostic and surveillance colonoscopies in its analysis. Our criteria allow for our results to be more generalizable to average risk patients and more applicable to benchmark detection rates set for the screening population[11]. Another advantage was that our study was sufficiently powered compared to any other available literature similarly studying SSADR with HD colonoscopy to date[10,12].

In acknowledging the strengths to our data, it is also important to consider why this improvement to SSADR has not clearly been reflected in the overall ADRs in existing study on HD colonoscopy, as

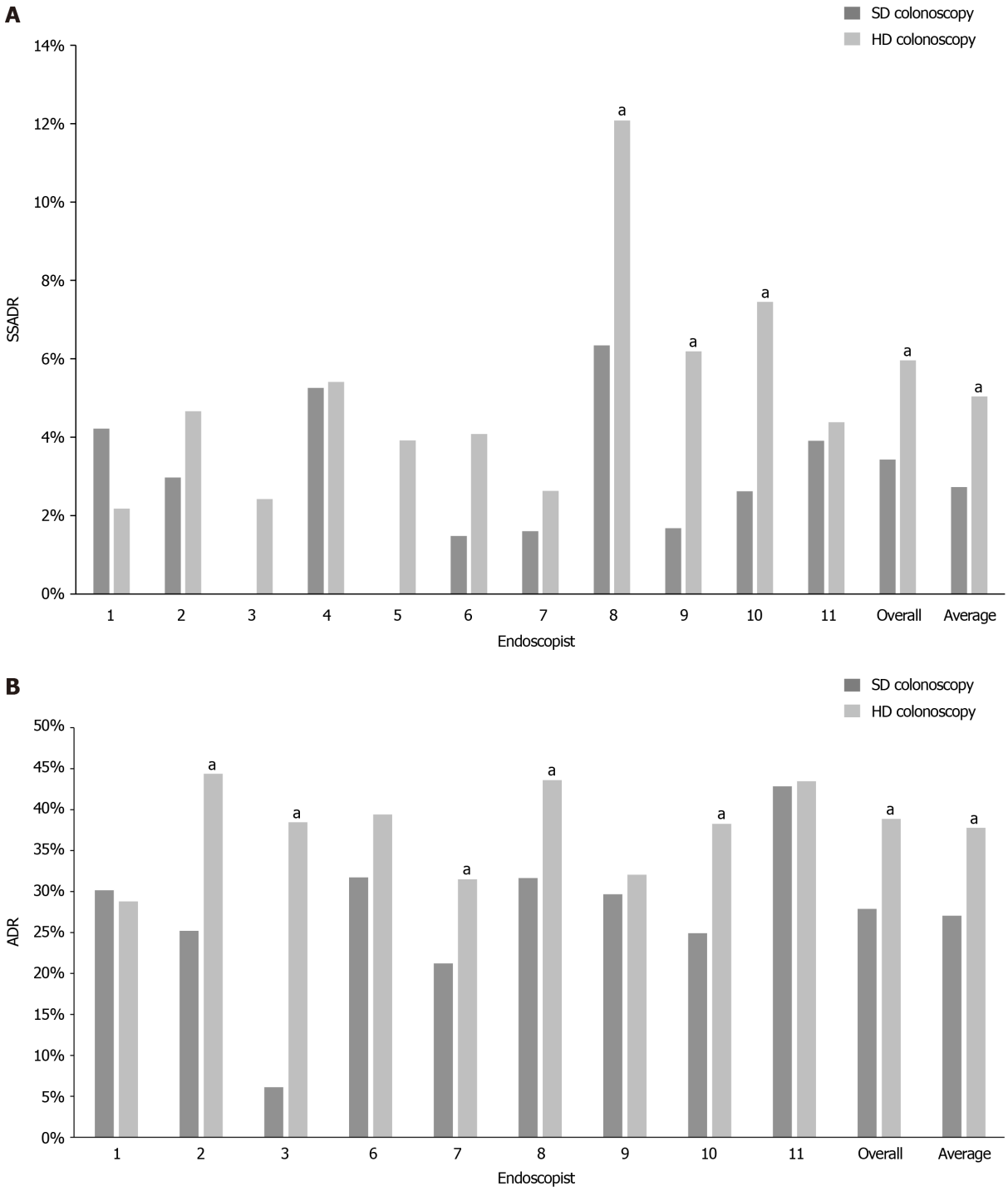

Figure 1 Endoscopist, overall, and average sessile serrated adenomas detection rates (A) and adenoma detection rates (B) during standard definition colonoscopy and high definition colonoscopy. [a]*P* < 0.05. SSADR: Sessile serrated adenomas detection rate; ADR: Adenoma detection rate; SD: Standard definition; HD: High definition.

demonstrated by the weak recommendation by the ESGE on the utility of HD colonoscopy[8]. It is possible that higher quality endoscopes have more utility in the detection of subtle SSA lesions than in the detection of adenomatous polyps that have been historically easier to identify, perhaps limiting the overall benefit of HD colonoscopy on detection of the conventional adenomas. Thus, as SSAs make up a relatively small component of overall ADR compared to conventional adenomas, the significant improvement to SSADR may be undetectable when assessing the improvement to all adenoma detection with HD colonoscopy. In this way, our results help to highlight a significant benefit of HD colonoscopy that may have been overlooked in prior studies of HD colonoscopy focused on overall ADR. This allows for stronger recommendations for the use of HD colonoscopy given that improved SSA detection is an unmet need in screening colonoscopy.

We acknowledge some limitations to our study. A main limitation is the retrospective design of the study. In addition, while the longitudinal nature of the study permitted a relatively large number of colonoscopies to be included in our analysis, the four-year period allowed for changing skill level of endoscopists over time. Another limitation is that our study did not control for withdrawal time. In studies past, this has been one factor that has been demonstrated to significantly improve SSADR with maximum benefit at 9 min of withdrawal time[4,5]. Nevertheless, the withdrawal times of our endoscopists may have been optimized on average as the mean withdrawal time of academic gastroenterologists has been reported to be 9.1 min[5,14]. Another consideration arises from a lack of control for bowel preparation quality in our study. Although two prior studies that have evaluated the impact of bowel preparation on SSA detection found a nonsignificant impact of bowel preparation on SSADR, a 2016 prospective study reported significant decrease in SSADR with bowel preparation quality that is below high quality in a population of veterans with high adenoma prevalence, suggesting that our study's lack of exclusion of colonoscopies with suboptimal bowel preparation may have falsely lowered our SSADR results[4,15,16]. We also acknowledge discrepancies of eligible colonoscopy totals for the SSADR data collected directly for this study and ADR data collected from a preexisting study at our center, likely due to differences in the manual review of eligible colonoscopies during respective data compilations. COVID-19 also significantly impacted elective procedures in 2020, reducing the number of colonoscopies in the HD colonoscopy group.

CONCLUSION

In conclusion, our study suggests that high definition colonoscopy significantly improves sessile serrated adenoma detection in the screening of average risk patients. By improving the detection and removal of these lesions, adoption of high definition colonoscopy may reduce the significant premalignant burden of sessile serrated adenomas.

ARTICLE HIGHLIGHTS

Research background

Sessile serrated adenomas (SSA) have become increasingly recognized as important premalignant lesions that are difficult to detect during colonoscopy due to similarity in appearance to surrounding colonic mucosa. Hypothesizing that higher resolution colonoscopy may improve SSA detection rates (SSADR), we performed a retrospective study to evaluate the impact of high definition (HD) colonoscopy compared to standard definition (SD) colonoscopy on SSADR during screening colonoscopy. To our knowledge, this study is the first to study the utility of HD colonoscopy for SSADR in average-risk patients. In the absence of a strong clinical guideline to obligate the use of HD colonoscopy, the benefit demonstrated to SSADR by HD colonoscopy in our study may help strengthen the evidence to recommend its use in all settings.

Research motivation

To our knowledge, there has been no study on the efficacy of HD colonoscopy *vs* SD colonoscopy on SSADR in average risk patients undergoing screening colonoscopy only. Furtheremore, the most recent position by the European Society of Gastrointestinal Endoscopy on the adoption of HD colonoscopy for overall adenoma detection in average risk patients is weak, citing inconsistent trial results, which may deter centers that currently use SD colonoscopy from adopting HD colonoscopy. Given the lack of data on the adoption rate of HD colonoscopy outside of tertiary care centers, proving the benefit of HD colonoscopy on the detection of premalignant SSAs, specifically, may help strengthen the evidence behind its use in all settings.

Research objectives

We performed a retrospective study to evaluate the impact of HD colonoscopy compared to SD colonoscopy on SSADR exclusively during screening colonoscopy. Our secondary analysis compared overall adenoma detection rates (ADR) with HD colonoscopy *vs* SD colonoscopy at our center. By demonstrating that high definition colonoscopy significantly improves sessile serrated adenoma detection in the screening of average risk patients, the adoption of high definition colonoscopy may be universally recommended to reduce the significant premalignant burden of sessile serrated adenomas.

Research methods

All colonoscopies performed at our tertiary medical center in the two years before and after the transition from SD colonoscopy to HD colonoscopy on June 2nd, 2018 were identified. For the primary SSADR analysis, each colonoscopy report and associated pathology report during the defined study

period were collected, from which patient demographics, colonoscopy date, colonoscopy indication, colonoscopy findings (polyp/Lesion presence and type), and endoscopist data were compiled. For the secondary analysis involving ADR, preexisting ADR data from our center with the same inclusion criteria during the same time period was used. The average age and the sex distribution of the SD colonoscopy group (June 1, 2016 – June 1, 2018) and the HD colonoscopy group (June 2, 2018 – June 2, 2020) were compared for demographic data, using only data from the SSADR analysis. The primary outcome measure were differences in individual endoscopist, overall, and mean SSA detection rate (SSADR) (defined as the proportion of eligible colonoscopies in which at least one SSA was identified) for the SD and HD colonoscopy periods. The secondary outcome measure was differences in individual endoscopist, overall, and mean overall adenoma detection rate (defined as the proportion of eligible colonoscopies in which at least one adenoma of any type was identified) for the SD and HD colonoscopy periods.

Research results

There was no significant difference in average age or sex distribution between the SD and HD groups. The mean SSADRs with SD colonoscopy and HD colonoscopy were 2.73% and 5.04%, respectively, yielding a statistically significant improvement of 2.30% (P = 0.00028). Comparison of the overall SSADRs also showed a statistically significant improvement from 3.43% with SD colonoscopy to 5.96% with HD colonoscopy (Δ 2.53%, P = 0.00849). On the individual level, three endoscopists experienced statistically significant benefit with HD colonoscopy (+5.74%, P = 0.0056, +4.50%, P = 0.0278, +4.84%, P = 0.03486). Preexisting ADR data was only available for nine of the eleven endoscopists. The mean ADRs with SD colonoscopy and HD colonoscopy were 27.06% and 37.77%, respectively, yielding a significant improvement of 10.72% (P = 0.01522). Comparison of the overall ADRs also showed a significant improvement with HD colonoscopy (Δ 10.98%, P < 0.00001). Most of the endoscopists demonstrated individual increases in ADR with HD colonoscopy. Five of these endoscopists saw significant benefit.

Research conclusions

To our knowledge, this study is the first to show the utility of HD colonoscopy for SSADR in average-risk patients, thereby demonstrating it as an important tool to improve the detection and removal of these premalignant lesions during routine colorectal cancer screening. Furthermore, in the absence of a strong clinical guideline to obligate the use of HD colonoscopy, the benefit demonstrated to SSADR by HD colonoscopy in our study may help strengthen the evidence to recommend its use in all settings.

Research perspectives

Future research endeavors should include randomized control trials to assess the efficacy of HD *vs* SD colonoscopy in average-risk patients undergoing screening colonoscopy only.

FOOTNOTES

Author contributions: Sehgal A, Aggarwal S, Mandaliya R, Loughney TM, and Mattar MC designed the research study; Sehgal A and Aggarwal S performed the research; Sehgal A collected and analyzed the data; Sehgal A and Aggarwal S wrote the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: As our retrospective study qualified as a quality improvement project, our institution did not require IRB approval for our study.

Informed consent statement: As our study was a quality-improvement study with retrospective chart review, informed consent was not necessary at our institution. Any and all details that might disclose the identity of the subjects included in our study were omitted.

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Observational Study

Endoscopic resection of superficial bowel neoplasia: The unmet needs in the Egyptian practice

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Abstract

BACKGROUND

Management of superficial bowel neoplasia (SBN) in early stages is associated with better outcomes. The last few decades experienced a paradigm shift in the management of SBN with the introduction of advanced endoscopic resection techniques (ERTs). However, there are no clear data about the aspects of ERTs in Egypt despite the growing gastroenterology practice.

AIM

To investigate the knowledge, attitude, and practice of ERTs toward management of SBN among Egyptian practitioners and the suitability of the endoscopy units' infrastructures toward these techniques.

METHODS

An online 2-pages questionnaire was used. The first page comprised demographic data, and questions for all physicians, about the knowledge (11 questions) of and attitude (5 questions) toward ERTs as a therapeutic option for SBN. The second page investigated the practice of ERTs by endoscopists (6 questions) and the infrastructures of their endoscopy units (14 questions). The survey was disseminated through July 2021 and the data were collected in an excel sheet and later analyzed anonymously.

RESULTS

The complete responses were 833/2300 (36.2%). The majority of the participants were males (n = 560, 67.2%), middle-aged (n = 366, 43.9%), consultants (n = 464, 55.7%), gastroenterologists (n = 678, 81.4%), spending ≥ 15 years in practice (n = 368, 44.2%), and were working in university hospitals (n = 569, 68.3%). The majority correctly identified the definition of SBN (88.4%) and the terms polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD) (92.1%, 90.2%, and 89.1% respectively). However, 26.9%, 43.2% and 49.5% did not recognize the clear indication of polypectomy, EMR, and ESD respectively. Although 68.1% of physicians are convinced about the ERTs for management of SBN; only 8.9% referred all candidate cases for ERTs. About 76.5% of endoscopists had formal training in the basic polypectomy techniques while formal training for EMR and ESD was encountered only in 31.9% and 7.2% respectively. About 71.6% and 88.4% of endoscopists did not perform EMR or ESD in the last one year. Consequently, the complication rate reported by endoscopists was limited to 18.1% (n = 103) of endoscopists. Only 25.8% of endoscopists feel confident in the management of ERTs-related complications and a half (49.9%) were not sure about their competency. Regarding the end-oscopy units' infrastructures, only 4.2% of the centers had their endoscopes 100% armed with optical enhancements and 54.4% considered their institutions ready for managing ERTs-related complications. Only 18.3% (n = 104) of endoscopists treated their complicated cases surgically because the most frequent ERTs-related complications were procedural bleeding (26.7%), and perforations (17%).

CONCLUSION

A significant deficiency was reported in the knowledge and attitude of Egyptian practitioners caring for patients with SBN toward ERTs. The lack of trained endoscopists in both EMR and ESD in part is due to unsuitable infrastructures of many endoscopy units.

Key Words: Endoscopic submucosal dissection; Endoscopic mucosal resection; Polypectomy; Superficial bowel neoplasia; Egypt

Core Tip: A paradigm shift in the management of superficial bowel neoplasia had been observed over the last few decades with the introduction of new endoscopic resection techniques and the advancements reported in the endoscopes and accessories. These advanced endoscopic resection techniques especially endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) necessitates the insertion of knowledge and improvement of the practice attitude of the practitioners before delivering education and training programs to skilled endoscopists. The current study investigated these aspects among Egyptian practitioners and it revealed a significant deficiency in the knowledge and attitude with lack of trained endoscopists in both EMR and ESD in part is due to unsuitable infrastructures of many endoscopy units.

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INTRODUCTION

The prevalence of bowel cancer is variable around the globe. Colon cancer ranks 3rd among all cancers while cancer stomach which has geographic predilection ranks 6th. Cancer colon ranks 2nd while cancer stomach ranks 4th regarding cancer-related death[1]. In Egypt there is no recent formal prevalence rate, however, early reports showed that colorectal cancer ranks 7th most common cancer among Egyptians [2].

Management of early bowel malignancy has been associated with better treatment outcomes; low morbidity and mortality. Over the last two decades, there was a paradigm shift in the management of early bowel malignancy[3,4]. Surgical resection had been the therapeutic option of choice. However, the major advancements in gastrointestinal (GIT) endoscopy evolved in the development of new endoscopic resection techniques (ERTs) as alternative curative options.

Across the literature, ERTs have been associated with better outcomes and improved quality of life in comparison to conventional surgical techniques[3,5]. Different ERTs are currently known and include the standard snare polypectomy techniques, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD). Each method had its indications, techniques, complications as well as training curve defined by many of the current practice guidelines[3,6,7].

In Egypt, there is a growing GIT endoscopy practice. Unfortunately, most of the institutions lack formal training programs for junior gastroenterologists. Consequently, no clear data are evident about the current practice of endoscopic resection techniques. We believe that investigating the current aspects of ERTs would alarm; currently and guide; in the near future, the practice as well as the training of advanced resection techniques among Egyptian practitioners. The current study aimed at investigating the knowledge, attitude, and practice of endoscopic resection techniques among Egyptian practitioners managing patients with SBN as well as the suitability of the infrastructures in the endoscopy units toward these techniques.

MATERIALS AND METHODS

Questionnaire development

An online questionnaire was developed and designed only for Egyptian physicians caring for patients with SBN. Besides the demographic data (gender, age, career specialty, the main hospital of practice, *etc.*) in this questionnaire (Supplementary Material), four domains were investigated: (1) Knowledge about the cancerous process of the bowel and its management options, either from authorized websites as international guidelines or real experience (11 questions); (2) Attitude toward (5 questions) ERTs as an acceptable therapeutic option for management of SBN; (3) Practice of ERTs (6 questions); and (4) infrastructures of the national endoscopy units (manpower, endoscopes, accessories, policy, and procedures): One of the important determinants for performing ERTs are infrastructures of the endoscopy units (14 questions)

For all physicians (non-endoscopists and endoscopists), the knowledge about and attitude toward ERTs were assessed while endoscopists only were surveyed for their practice and the infrastructures of their endoscopy units

The questionnaire dissemination

The survey was disseminated through 3 main channels: First, through 2 WhatsApp groups for national gastroenterology physicians. Second, through emails of the national societies for gastroenterologists, internists, and surgeons. Third, through Facebook accounts of the relevant groups. The survey was disseminated through July 2021. A reminder announcement and emails were sent again one week before the closure of the survey. The responses were collected in an online platform (2 online pages; the first page focused on demographic data, knowledge, and attitude while the second page comprised data for endoscopists; evaluating the skills in practice and the infrastructures of their endoscopy units). The data were exported to an excel sheet and were analyzed later anonymously.

Participants

Egyptian physicians manage patients with gastroenterology problems (gastroenterologists, internists, and surgeons).

Sample size calculation

The primary objective of this study was to measure the knowledge, attitude, and practice among Egyptian physicians caring for patients with SBN. Consequently, we tried to reach as many physicians as we can without fixing a sample size, aiming that a large number of recruited physicians improve the reliability of the results.

Ethical considerations

In this survey form, all participants were informed about the volunteer role to participate. The data were analyzed anonymously and the data of participants were not disclosed. The institutional review board of Kafrelsheikh University approved the questionnaire (approval code MKSU code 36-9-21).

Statistical analysis

The data were collected and analyzed using Statistical Package for Social Sciences (SPSS version 26.0) software (IBM SPSS Inc. Chicago, United States). There were no incomplete responses to be excluded from the analysis. The data were expressed as numbers and proportions.

RESULTS

Study participants

In this survey, about 2300 Egyptian physicians were invited. The complete responses were obtained from 833/2300 with a percentage of 36.2%. There were no missing responses from visitors to the first page of the questionnaire (the measure of knowledge and attitude among endoscopists and non-endoscopists) nor to the second page of the questionnaire (endoscopists). About two-third of the participants were males (560, 67.2%) and the majority were middle-aged between 36-45 years (n = 366, 43.9%), were consultants (n = 464, 55.7%), and were gastroenterologists (n = 678, 81.4%). The majority were experienced in practice; spending more than 15 years in practice (n = 368, 44.2%), and about two-third also were working in university hospitals (n = 569, 68.3%) (Table 1).

Although the respondents represented the 4 major regions of Egyptian practice (Cairo, Alexandria, Nile Delta, Upper Egypt), some regions were not represented in the responses *e.g.* the region of Sinai and Suez Canal. More details are shown in Supplementary Table 1.

Knowledge

Although the current survey demonstrated that 88.4% of the physicians correctly identified the SBN as a cancerous process of the bowel that is limited to the mucosa and submucosa, 34.3% and 36.9%of them missed the correct diagnostic (different endoscopic methods) and therapeutic (ERTs) maneuvers for SBN, respectively. These findings explain why 43.2% of the surveyed practitioners failed to describe the different therapeutic modalities for bowel cancer in general. More details about the correct and incorrect responses are shown in Table 2.

The majority of the surveyed physicians identified what is meant by polypectomy, EMR, and ESD correctly in 92.1%, 90.2%, and 89.1% respectively. However, a substantial proportion of them lacks the correct knowledge about the endoscopic treatment for mucosal lesions and the lack of recognition of the correct answer parallels the complexity of the maneuver. For polypectomy, 26.9% did not recognize that endoscopic treatment of pedunculated polyp is snare polypectomy, compared to 43.2% who did not correctly recognize EMR as the standard endoscopic resection technique for non-pedunculated lesions ≤ 15 mm. Furthermore, the frequency rises to 49.5% when ESD was investigated as the endoscopic resection technique for non-pedunculated lesions ≥ 20 mm. Consequently, 28.5% of the surveyed physicians did not recognize the spectrum of indications of ERTs to involve Barrett's high dysplasia, polyps, and SBN (Table 2).

Attitude

Early diagnosis of SBN necessitates picking up cases so early before even any manifestations develop; consequently, screening of average-risk population and/or surveillance of high-risk patients is necessary. However, the screening policy seems deficient in Egyptian practice. According to the personal attitude toward the SBN measured in the current questionnaire by 5 questions, only 15.1% of physicians refer all candidates of screening for endoscopic surveillance. Furthermore, 12.2% of the physicians did not refer the high-risk patients for endoscopic screening, the main bulk of practitioners (72.6%) invariably refer the candidates for screening (Table 3).

Although 68.1% of physicians are convinced about the ERTs as management for SBN; only 8.9% of them refer all candidate cases for ERTs which represents a sort of reluctance in the decision making. When SBN is suspected/confirmed endoscopically only 14.4% of practitioners refer their patients for surgical resection and surprisingly 17.6% did not refer them for surgical resection at all and the main bulk of the surveyed physicians (68%) prefer the patients to resection with variable frequencies (Table 3).

Table 1 Demographic characteristics of the surveyed physicians

Variable	Frequency (*n* = 833)	Percent (%)
Gender		
Male	560	67.2
Female	273	32.8
Age (yr)		
≤ 35	276	33.1
36-45	366	43.9
> 45	191	22.9
Academic categories		
Consultants	464	55.7
Residents	36	4.3
Specialist	333	40.0
Career specialty		
Gastroenterologist	678	81.4
General medicine	121	14.5
Surgery	34	4.1
Years of practice (yr)		
< 5	145	17.4
5-10	120	14.4
10-15	200	24.0
> 15	368	44.2
Main hospital of practice		
Central	80	9.6
General	111	13.3
Teaching institution	73	8.8
University	569	68.3

It seems that the above-mentioned attitude toward endoscopic detection and endoscopic management of SBN is related to individual opinions and behavior because most of the institutions (62.2%) are lacking for panels discussing the management of SBN.

Practice

About two-third of the surveyed physicians were endoscopists (*n* = 570, 68.4%). More than two-third of the endoscopists had formal training in the basic polypectomy techniques (67.5%), while formal training focusing on the advanced ERTs namely EMR and ESD was encountered only in 31.9% and 7.2% respectively which represents a substantial deficiency in training for the advanced ERTs in the Egyptian community. Although most of the endoscopists (58.1%) are familiar with the Paris classification for reporting SBN, only 34.9% are popular with or using Kudo classification, and only 10.5% of endoscopists use other classification systems in reporting their lesions. About two-third (63.7%) were aware of the causes that increase the submucosal fibrosis which ultimately affect the success rates of advanced ERTs (Table 4).

Regarding the personal/individual skills (Table 5) for ERTs, a substantial number of the surveyed endoscopists (67.4%) did not excise polyps in the last year, although the cause is not clear this probably reflects the low prevalence of bowel neoplasia in the Egyptian community. This seems accepted because 71.6% did not perform EMR in the last year and 88.4% of the endoscopists did not perform ESDs in the last year. Consequently, it is accepted that the complication rate reported by endoscopists was limited to 18.1% (*n* = 103) of endoscopists. An alarm reported in the current survey is the competency in management of ERTs-related complications. Only 25.8% of endoscopists feel confident in the management of complications and nearly half of the surveyed endoscopists (49.9%) are not sure about their competency.

Table 2 Assessment of knowledge among the surveyed physicians

Variable	Number	Percent
What is superficial bowel neoplasia?		
True	736	88.4
False	97	11.6
Superficial bowel neoplasia can be diagnosed with?		
True	547	65.7
False	286	34.3
What is the best option for the treatment of bowel cancer in general?		
True	473	56.8
False	360	43.2
What is the best treatment for superficial bowel neoplasia?		
True	526	63.1
False	307	36.9
What does polypectomy mean?		
True	767	92.1
False	66	7.9
What does EMR stand for?		
True	751	90.2
False	82	9.8
What does ESD stand for?		
True	742	89.1
FalseE	91	10.9
The best endoscopic treatment option for pedunculated polyps		
True	609	73.1
False	224	26.9
The best endoscopic treatment option for non-pedunculated lesions ≤ 15 mm in diameter		
True	473	56.8
False	360	43.2
The best endoscopic treatment option for non-pedunculated lesions ≥ 20 mm		
True	421	50.5
False	412	49.5
Endoscopic resection is a suitable treatment?		
True	596	71.5
False	237	28.5

Infrastructures of the national endoscopy units

One of the important determinants for performing ERTs is infrastructure of the endoscopy units, which was focused in the current survey (Table 6).

Manpower: About 70.2% (n = 400) of the surveyed endoscopists had ≥ 5 independent endoscopists in their units, which means a suitable number of endoscopists to deliver training in each unit. However, most of the nursing staff (52.1%) are not formally trained for advanced resection techniques.

Endoscopes and accessories: About 54.4% of the endoscopists see that the total number of endoscopes in their units is not sufficient to perform the daily endoscopic procedures including the ERTs. Furthermore, the endoscopes with optical enhancements (NBI, i-SCN, FICE) are lacking in 23.7% of

Table 3 Attitude of the surveyed physicians towards superficial bowel neoplasia

Question (%)	Frequency	Percent
How frequently do you refer your patients for endoscopic screening of superficial bowel cancer in high-risk groups? (% of the high-risk patients you see)		
0	102	12.2
25	386	46.3
50	116	13.9
75	103	12.4
100	126	15.1
How convinced you are with endoscopic treatment of superficial bowel cancer?		
Convinced	567	68.1
I don't Know	175	21
Not convinced at all	91	10.9
How frequently do you refer a patient with endoscopic features of superficial bowel cancer for endoscopic resection? (% of the patients you see)		
0	235	28.2
25	301	36.1
50	115	13.8
75	108	13
100	74	8.9
How frequently do you refer a patient with endoscopic features of superficial bowel cancer for surgical management? (% of the patients you see)		
0	147	17.6
25	290	34.8
50	212	25.5
75	64	7.7
100	120	14.4
In your institution do you have a panel to discuss the treatment options for superficial bowel neoplasia?		
No	518	62.2
Yes	315	37.8

endoscopy theaters, and 42.5% had ≤ 25% of the endoscopes with optical enhancement which means a deficiency of magnification facility and diminished probability of accurate diagnosis while only 4.2% of the centers had their endoscopes 100% armed with optical enhancements. More than two-third of the centers had advanced diathermy units (68.2%), meanwhile, argon plasma coagulation and haemoclips available to enable resections and guard against adverse events were available in 89.3% and 86.1%, respectively. Again the probability of diagnosis seems defective if relied on chromoendoscopy because only 20.2% of endoscopists had in their units the dyes for chromoendoscopy and tattooing.

Procedure: Focusing on the procedures, most centers (80.7%) perform ERTs under anesthesiologist observation. Furthermore, 72.5% of endoscopists reported that a surgical back up team is available for management of complications and that is why 54.4% of them decided that their institutions are ready for managing complications following ERTs. Only 18.3% (n = 104) of endoscopists treated their complicated cases surgically, because the most frequent complication during ERTs was procedural bleeding (26.7%), and perforations were the second common complication (17%).

DISCUSSION

In fact, the last 2-3 decades experienced a paradigm shift in the endoscopic management of SBN in particular for the colonic lesions due to the advancements in magnification endoscopy (imaging), introduction of CO_2 insufflation and the advent of modern electrosurgical devices with adoption of new techniques mainly EMR and ESD. Both have been associated with improved patient oriented outcomes

Table 4 Basic endoscopic practice knowledge for endoscopic resection techniques among the surveyed endoscopists

Question	Number (N = 570)	Percentage (%)
Are you trained formally on endoscopic polypectomy?		
No	134	23.5
Yes	436	76.5
Are you trained formally on EMR?		
No	388	68.1
Yes	182	31.9
Are you trained formally on ESD?		
No	528	92.6
Yes	42	7.4
Do you use Paris classification in reporting the lesions?		
No	239	41.9
Yes	331	58.1
Do you use Kudo classification in reporting the lesions?		
No	371	65.1
Yes	199	34.9
Do you use classifications other than Paris and Kudo in reporting the lesions?		
No	510	89.5
Yes	60	10.5
Which of the following practices increase sub-mucosal fibrosis and hence affect the success of advanced endoscopic resection techniques		
All apply	363	63.7
Extensive biopsies	117	20.5
Partial snare polypectomy	24	4.2
Tattoo injection for marking immediately under or close by a lesion	66	11.6

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

with improved quality of life and that is why a growing interest in such techniques became rapidly a global era.

However, these advanced techniques are not widely available in all endoscopy units and need special advanced training. Furthermore, we believe that certain communities may lack the basic knowledge and practice attitude toward these techniques as the currently preferred management for early stages of bowel neoplasia in comparison to the surgical excision and this was the rationale to investigate the Egyptian practice about these high-quality ERTs. To the best of our knowledge, this is the first trial to estimate different aspects of ERTs in the Egyptian community.

In this study, the knowledge among the physicians managing patients with SBN was not sufficient, especially in the area of endoscopic diagnosis and the clear indications of each technique. Furthermore, there was also a deficiency in the knowledge of the spectrum of indications for ERTs, although the description of the proper diagnostic and management approach to SBN and description of such techniques and their indications are defined by many of the published practice guidelines[3,8].

According to the current survey, there was an obvious reluctant attitude at both institutional and individual levels. Most of the Egyptian institutions lack panels discussing the management of SBN. The individual reluctance is obvious not only in the endoscopic screening of high-risk patients and hence early recognition of SBN[9], but also clear in the lack of referring all candidate patients for ERTs although most of the physicians are convinced in ERTs.

In fact, the knowledge and attitude to ERTs have not -to the best of our knowledge- been investigated previously, yet did the current survey and we identified a reasonable deficiency in the knowledge and deviation of the attitude of the surveyed physicians. The barriers to knowledge and attitude vary and are not limited to; lack of sufficient time to access the educational materials[10], lack of funds[11], among others. We believe that delivering educational materials focusing on these techniques and supplying reports with documented efficacy of such techniques in the management of SBN with its

Table 5 Individual competency in endoscopic resection techniques among the surveyed endoscopists

Question	Number (N = 570)	Percentage (%)
How many polyps did you excised in the last year?		
0	384	67.4
11-20	96	16.8
21-30	30	5.3
41-50	36	6.3
Less than 10	12	2.1
More than 50	12	2.1
How many EMRs did you perform in the last year?		
0	408	71.6
10-20	48	8.4
20-30	12	2.1
Less than 10	102	17.9
How many ESDs did you perform in the last year?		
0	504	88.4
10-20	12	2.1
Less than 10	54	9.5
How many complications from endoscopic resection techniques have you had in the last year (% of your total cases)?		
0	329	57.7
0.25	91	16.0
0.5	12	2.1
I don't practice advanced endoscopic techniques	138	24.2
How competent are you in managing the complications of endoscopic resection techniques?		
Competent	147	25.8
I am not sure	284	49.8
Non-competent	139	24.4

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

impact on the quality of life among the patients would improve both the knowledge and attitude among the Egyptian practitioners. This was proved in previous reports in other practice topics, for example, the knowledge and attitude of students and healthcare professionals was effectively improved through the delivery of teaching materials through different means ranging from face-to-face learning seminars, lectures and curricula[12], attending online curriculum[13], sending regular SMS to the practitioners [14], disseminating leaflets and hand-outs[15], and allowing quick *e.g.* through mobile phones, access to online resources[16].

In the current study, the barriers to knowledge and attitude toward ERTs in the management of SBN were not investigated. However, some data from previous reports can be inferred. These barriers are not limited to lack of evidence with limited belief in the value of available tools[17], because 78.1% of physicians are convinced about ERTs, or to lack of effective collaboration and teamwork skills[17], which is a growing interest in our practice, but rather extend to lack of formal education programs, the reluctance of sticking to the application of the guidelines and probably also to lack of continuous clinical audits[18].

The door is then open for the national leaders in the field to deliver these educational materials in the local conferences and meetings that run in the country over the year. In addition, directors of the gastroenterology curricula are responsible to insert these data in the course syllabus to be an integral part of the topic rather than an advancement delivered only to the subgroup of experts performing endoscopy. This has been proved effective per reports from Asia that proved improvement in the knowledge of practitioners toward early diagnosis and management of SBN after delivering structured training programs[8].

Table 6 Parameters of the endoscopy units' infrastructures among the surveyed endoscopists

%	Number (*n* = 570)	Percent
How many independent endoscopists are in your unit?		
Less than 5	170	29.8
5-10	164	28.8
More than 10	236	41.4
The nursing staff in your endoscopy unit are knowledgeable and trained on endoscopic resection techniques		
No	297	52.1
Yes	273	47.9
How sufficient is the number of endoscopes in your unit to perform all endoscopy duties?		
I am not sure	36	6.3
Not- Sufficient	310	54.4
Sufficient	224	39.3
How many endoscopes with optical enhancement (NBI- i-SCAN- FICE) are available in your unit (% of the total scopes in your unit)		
0.00	135	23.7
25.00	242	42.5
50.00	126	22.1
75.00	43	7.5
100.00	24	4.2
Dyes for chromoendoscopy are available in your unit		
No	455	79.8
Yes	115	20.2
Advanced Diathermy unit with different endoscopy modes is available in your unit		
No	181	31.8
Yes	389	68.2
APC is available in your unit		
No	61	10.7
Yes	509	89.3
Haemoclips are available in your unit		
No	79	13.9
Yes	491	86.1
In your endoscopy unit, the endoscopic resection techniques are operated under anesthesiologist's observation		
No	110	19.3
Yes	460	80.7
The most commonly reported complications from endoscopic resection techniques in your unit		
Delayed bleeding	24	4.2
Perforations,	97	17.0
Procedural bleeding	152	26.7
Sedation or anesthesia-related	12	2.1
We do not perform advanced endoscopic resection	285	50.0
Your institution is ready for managing the complications of endoscopic resection techniques?		
I am not sure	218	38.2
No	42	7.4

Yes	310	54.4
The surgical backup team is usually ready to manage complications of your cases		
No	157	27.5
Yes	413	72.5
How many complicated cases following endoscopic resection treated under surgical repair in the last one year within your institution (% from complicated cases)		
0.00	430	75.4
25.00	74	13.0
50.00	30	5.3

Per the current survey, a deficiency was reported not only in training for but also in performing ERTs, especially EMR and ESD. Furthermore, a small number of endoscopists are popular or using endoscopic classification systems and a reasonable number lack the competency in facing ERTs-related complications. The high-quality practice in ERTs relies on many pillars, the most important among it is training. Many endoscopic societies[3,19] formulated stepwise training curves for such procedures. It seems that an endoscopist should pass in the training curve from the basic polypectomy techniques to EMR and later to ESD in parallel with the advanced techniques. This could explain the results of the current survey. In an ascending frequency; polypectomy, EMR, and ESD were performed by Egyptian endoscopists at rates of 32.6%, 28.4%, and 11.6% respectively because this matches the complexity of each. Furthermore, the centers offering training for both EMR and ESD are very limited. However, the standard polypectomy is more popular, less technically demanding, and hence was the commonly practiced technique among the surveyed.

The delivery of high-quality resection techniques needs a recognized skill in delivering the resection and in managing the complications, especially the bleeding and perforation not only at an individual endoscopist level but rather very important at an institutional level. This emphasizes the importance of a teamwork management plan including basically an endoscopist, surgeon, anesthesiologist, and interventional radiologist. Favorably, there is a growing trend in the Egyptian practice toward teamwork activities for many GIT case scenarios including ERTs although in its early milestones.

The availability of skilled endoscopists is the stone cornerstone of performing ERTs. Their availability guarantees not only delivering a high-quality resection, but also a training platform to the possible trainees. Although, the current survey revealed recognized skills in the standard polypectomy, it did reveal a fair experience in EMR and very limited skilled endoscopists in ESD, and it also revealed a lack of competency in the management of ERTs-related complications. This should alarm the stakeholders for the urgent need to establish training centers and exchange experience with worldwide leaders in advanced endoscopy to train a new generation of Egyptian gastroenterologists in ERTs. In Egypt, we have a few endoscopy workshops that usually operate such cases both as hands-on training on models and live transmission of real cases but this seems non-sufficient solely in delivering the desired training, although it is important.

Although EMR was introduced before ESD, the experience in its application still needs training and assurance of competency. This ultimately grantee quality and improved patient outcomes. This needs to be inserted in post-graduate courses and continuing education settings[20].

One recently published report surveyed Korean endoscopists showed that both observation and performing ESD under direct supervision were the most important determinants of ESD training[21]. The authors reported also that, hands-on-courses were implemented by all the training centers. It is worth mentioning that in Korea at least 45 centers implement formal ESD practice and training in comparison to very few centers in Egypt. The problem of delivery of a formal training program for advanced resection techniques such as ESD has its own reasons that vary from the far East to the West and are not limited to trainees' background, differences in the type of the pathology seen, the availability of highly qualified mentors and training centers, availability of high-quality endoscopes among others[22]. Hence, it is expected to have a global shortage in training for ESD and not only in Egypt and Middle East countries.

The infrastructures (both in equipment, procedures, and skilled personnel) of endoscopy units nationwide need improvements. Most of the endoscopy centers are not equipped with enough scopes and specifically, the units lack advanced scopes with optical enhancements. The procedures with the availability of surgical backup teams look accepted, however, there was a shortage in the formal nurse training.

In the Egyptian community, tertiary referral centers (university hospitals, teaching institutions) are rather equipped than the general and central hospitals as per the data from the current survey. Consequently, these centers offer most of the national daycare service and training. However, focusing on EMR and ESD very few centers are currently delivering the service for real cases with a very limited number of trainees. Hence, we can deliver a very important message to the local health authorities for

the necessity to equip endoscopy units nationwide with the required equipment and establish multidisciplinary teams for managing cases of SBN and running formal training programs.

The plan is to deliver lectures in the meetings, conferences to insert the knowledge and improve the attitude among all physicians caring for patients with SBN. Later on, endoscopists can have a rising training curve that begins with hands-on courses[21], on *ex vivo* models[23-25] and *in vivo* on the animals[25,26], then trainee needs to watch videos, attend live cases, observes and assist in cases and finally perform under direct supervision. Implementation of this step-up fashion of training will enable trainees to learn early and to have a great chance to had supervised techniques[27,28]. Both have been associated with trainee satisfaction in previous studies[21]. Although attendance of conferences, meetings, face to face theoretical courses, watching recorded videos, attending live cases demonstrations are essential to improve knowledge and attitude, performing these advanced techniques under direct supervision by experts seems the most important method of training and hence we encourage our local leaders to propose a teaching and training algorithms in certified centers that end with practice and performance of ERTs under direct supervision by experts. This, ultimately fill the missing gaps in Egyptian practice.

This study had some limitations. First, include use of non-gastroenterologists. In fact, evaluation of knowledge and attitude of non-gastroenterologists is very essential because they constitute an integral role of care and sometimes are the first relay in delivering the care for patients with SBN and that is why there was a generalization in the questions of the knowledge domain. Second, lack of coverage for some geographic areas in the country. We distributed the questionnaire aiming at covering the whole country but usually, the response rates from the online questionnaires are limited due to many reasons. Third, the is a non-inclusion of the private sector. Currently, the law is not allowing practicing endoscopy in private clinics. However, endoscopy still running in private hospitals although it is sometimes difficult to assess the private sector due to many reasons including but not limited to the heterogeneity of the working endoscopists. Fourth, we did not investigate the barriers to the deficiency in all aspects focused. These can be focused on future surveys.

CONCLUSION

In conclusion, to the best of our knowledge, this is the first survey to focus ERTs status in Egypt and despite the limitations we have, this survey revealed a significant deficiency not only in the knowledge and attitude of Egyptian practitioners caring for patients with SBN toward ERTs, but it also spotted the light on the lack of trained endoscopists in both EMR and ESD in part due to unsuitable infrastructures of many endoscopy units around the country. These findings would enforce stakeholders for the urgent need to deliver educational and training programs focusing ERTs hand in hand with improving the infrastructures of the endoscopy units. Stakeholders of gastroenterology practice in Egypt are asked to improve all aspects of practice. They should focus on giving basic knowledge, improve the attitude of practitioners before giving the advanced training and supply the required infrastructures.

ARTICLE HIGHLIGHTS

Research background

Stakeholders of gastroenterology practice in Egypt are asked to improve all aspects of practice. They should focus on giving basic knowledge, improve the attitude of practitioners before giving the advanced training and supply the required infrastructures. The barriers to the deficiency in all aspects of primary and secondary outcomes can be focused on in future surveys.

Research motivation

Our study concluded that lack of knowledge towards endoscopic resection techniques (ERTs), reluctant attitude, lack of well-trained endoscopists, and shortage of infrastructures are the main obstacles that hamper performing endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) on wider scale and on a routine basis in Egypt.

Research objectives

Complete responses were 833/2300. The majority correctly identified the definition of superficial bowel neoplasia (SBN), the terms polypectomy, EMR, and ESD (88.4%, 92.1%, 90.2%, and 89.1% respectively). However, 26.9%, 43.2%, and 49.5% did not recognize the clear indications of polypectomy, EMR, and ESD respectively. Although 68.1% are convinced about the ERTs; only 8.9% referred all candidate cases for ERTs. About 76.5% of endoscopists had formal training in the basic polypectomy techniques while formal training for EMR and ESD was encountered only in 31.9% and 7.2% respectively. About 71.6% and 88.4% of endoscopists did not perform EMR or ESD in the last year. Only 25.8% of endoscopists feel confident in the management of ERTs-related complications. Only 4.2% of the centers had their

endoscopes 100% armed with optical enhancements.

Research methods

This observational study began with the development of a questionnaire during May and June 2021, after agreement upon it an online 2-page questionnaire was developed and distributed through July 2021. The questionnaire was distributed through social media including WhatsApp and Facebook as well as emails from the national relevant scientific groups. The study focused on Egyptian physicians caring for patients with gastrointestinal health problems

Research results

The primary aim of our study was to assess the knowledge and attitude of Egyptian physicians caring patients with SBN toward the ERTs as potential curative methods. Furthermore, the practice of Egyptian endoscopists practicing ERTs was also investigated. The secondary endpoint was to assess the infrastructure of the endoscopy units regarding the manpower, scopes, and accessories, as well as policies within.

Research conclusions

In Egypt we have a growing endoscopy practice, however little is known about physician knowledge, attitude, and practice toward ERTs. Furthermore, the nationwide spread of endoscopy units needs to be explored as regards the suitability to run these advanced techniques.

Research perspectives

There is a global era in the management of SBN due to the introduction of advanced ERTs mainly EMR and ESD.

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FOOTNOTES

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REVIEW

Percutaneous endoscopic gastrostomy and jejunostomy: Indications and techniques

Alessandro Fugazza, Antonio Capogreco, Annalisa Cappello, Rosangela Nicoletti, Leonardo Da Rio, Piera Alessia Galtieri, Roberta Maselli, Silvia Carrara, Gaia Pellegatta, Marco Spadaccini, Edoardo Vespa, Matteo Colombo, Kareem Khalaf, Alessandro Repici, Andrea Anderloni

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Abstract

Nutritional support is essential in patients who have a limited capability to maintain their body weight. Therefore, oral feeding is the main approach for such patients. When physiological nutrition is not possible, positioning of a nasogastric, nasojejunal tube, or other percutaneous devices may be feasible alternatives. Creating a percutaneous endoscopic gastrostomy (PEG) is a suitable option to be evaluated for patients that need nutritional support for more than 4 wk. Many diseases require nutritional support by PEG, with neurological, oncological, and catabolic diseases being the most common. PEG can be performed endoscopically by various techniques, radiologically or surgically, with different outcomes and related adverse events (AEs). Moreover, some patients that need a PEG placement are fragile and are unable to express their will or sign a written informed consent. These conditions highlight many ethical problems that become difficult to manage as treatment progresses. The aim of this manuscript is to review all current endoscopic techniques for percutaneous access, their indications, postprocedural follow-up, and AEs.

Key Words: Percutaneous endoscopic gastrostomy; Enteral nutrition; Gastrostomy;

Percutaneous endoscopic jejunostomy; Indications and techniques

Core Tip: Percutaneous endoscopic gastrostomy (PEG) represents the first choice for long-term enteral nutrition support. The aim of this manuscript is to provide a comprehensive overview of PEG placement, including indications, contraindications, preprocedural clinical assessment, endoscopic techniques, adverse events, and postprocedural follow-up. Furthermore, endoscopic procedures for jejunal nutrition are also addressed. In consideration with the increasing frequency with which PEG placements are requested, this review may be a useful tool for clinical guidance both for endoscopists and physicians in different fields, with a particular focus on appropriateness of the indications and safety of this procedure.

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INTRODUCTION

Nutritional support is essential in patients who have a limited capability to maintain their body weight with a normal diet. In best practice, oral feeding is the main approach to choose for these patients[1]. Many patients cannot consume food by mouth. In some cases, oral intake can even be dangerous for patients with neurological conditions or obstructive causes, although their gastrointestinal (GI) tract is functional[2]. In these cases, physicians can support alimentary intake by positioning a nasogastric or nasojejunal tube or creating a direct access into the stomach through a percutaneous endoscopic gastrostomy (PEG)[3]. This allows the maintenance of normal physiological activities of the GI tract in order to avoid alterations in the intestinal barrier functions and long-term complications related to intravenous nutritional support[4,5].

The choice between whether the feeding tubes are placed *via* oral route over a PEG needs to be evaluated case-by-case by a multidisciplinary team, considering there are multiple factors related to procedural indications, such as patient condition, clinical scenario, and risk of adverse events (AEs) for the patient. However, when the GI tract does not work properly, such as in cases of obstruction, intravenous nutritional support should be preferred.

Parenteral nutrition (PN) is a nutritional support therapy that is provided through the intravenous administration of nutrients such as glucose, electrolytes, amino acids, lipids, and vitamins. Moreover, PN can be associated with AEs and is poorly tolerated, especially in patients with heart failure, renal insufficiency, and diabetes mellitus[6]. A recent systematic review with meta-analysis based on oncologic patients reported no differences between enteral nutrition (EN) and PN with regards to nutritional outcomes, with a higher incidence of infections in the PN group [risk ratio = 1.09, 95% confidence interval: 1.01-1.18; P = 0.03][7]. For these reasons, the recent European Society for Clinical Nutrition and Metabolism guidelines recommended administering total PN only when patients are unable to reach their nutritional outcomes with oral nutrition or EN[6]. Although the benefit of percutaneous access for EN have been reported for a while, several controversies and major concerns still exist regarding these procedures and the related AEs. The aim of this manuscript is to review all current techniques for percutaneous access for EN, their indications, postprocedural follow-up, and AEs.

INDICATIONS

Nowadays, many diseases result in long-term reduction of caloric intake. For this reason, placement of a percutaneous endoscopic access is needed in order to improve nutritional conditions. Percutaneous endoscopic nutrition can be achieved by either a transgastric approach through PEG or a transjejunal approach, namely percutaneous endoscopic jejunostomy (PEJ).

Ever since the first endoscopic insertion of a gastrostomy[8], there has been a worldwide diffusion of these techniques and an increase in indications for this medical approach. A summary list of indications for PEG placement is reported in Table 1. However, nutritional support is often only necessary for a short period, such as less than 1 mo, in case of stroke with fast recovery, mild head trauma, acute

pancreatitis, post-head and neck surgery, post-upper GI surgery, and other temporary diseases. In these patients, a nasogastric tube is easier to insert and to manage directly at bedside. On the other hand, some patients need nutritional support for longer periods of time.

In the recently published European Society of Gastrointestinal Endoscopy guidelines regarding endoscopic management of enteral tubes in adult patients, it is recommended to consider EN by percutaneous access when nutritional support is needed for more than 4 wk on a case-by-case basis[3]. The 4-wk cut-off is arbitrary and has been chosen to avoid many AEs that are related to percutaneous access (*e.g.*, infections). When indicated, the gastric route through a PEG is more desirable than the jejunal approach, due to its better tolerance, ease of procedure, and its possibility to be performed bedside[9]. In the case of altered anatomy, delayed gastric emptying, gastric outlet obstruction, duodenal obstruction, severe gastroesophageal reflux, or increased risk of aspiration pneumonia, PEJ must be considered[9].

Benign diseases

Neurological diseases often need nutritional support, especially in patients that cannot consume food orally due to neurological injury. Specifically, dementia is a common disease that needs EN. Patients with dementia often cannot or will not swallow. This condition mainly occurs later in the course of the disease when patients are in an advanced stage[10] and when they cannot express their will[11]. Currently, studies about EN in patients with dementia are scarce. A systematic review regarding patients with final stage dementia did not show differences between EN and no nutritional support in terms of survival, quality of life, nutritional status, function, behavior, or psychiatric symptoms[12]. For these reasons, the recently published European Society of Gastrointestinal Endoscopy guidelines recommend avoiding PEG placement in patients with advanced dementia, especially if they have a life expectancy of less than 4 wk[3].

Stroke is another common neurological cause of dysphagia, with an incidence of 23%-50%[13]. Some patients recover slowly or do not have the capability to consume food through the oral route, leading to a high risk of aspiration pneumonia and low nutritional intake. Motor neuron diseases often involve varying swallowing functions[14]. A recent cohort study on 957 patients (278 with PEG) affected by amyotrophic lateral sclerosis showed that PEG nutrition support improved overall survival expectancy (21 mo *vs* 15 mo, $P < 0.001$)[15]. Moreover, dysphagia can be present after head injury with neurological damage. A review focused on randomized controlled trials of nutrition in patients with head injury showed that survival expectancy and disability were improved by early PN or EN[16]. Patients with Parkinson's disease can develop motor alteration like dysphagia, and EN should be considered due to the increased risk of aspiration pneumonia and difficulties in oral intake[17].

There is poor evidence to support PEG placement in patients with other benign diseases such as cerebral palsy, anorexia, frailty, burn patients, and hypercatabolic diseases, even though each case must be evaluated individually. Furthermore, cases of PEG placement are reported in patients with benign esophageal strictures such as caustic stricture, Zenker diverticulum, post endoscopic therapy (endoscopic mucosal resection, endoscopic submucosal dissection, radiofrequency ablation), and achalasia[18,19].

Malignant diseases

Head and neck malignancies can lead to dysphagia in 35%-50% of cases[20]. The reported high-risk factors are hypopharyngeal localization, advanced neoplasia (T4), and combined chemoradiation. In these settings, the main indications for PEG are the onset of dysphagia, low nutritional intake, and loss of body weight[21]. A recent published study evaluated 130 patients with a head-neck tumor who underwent chemoradiotherapy. Of these, only 69 patients received a prophylactic PEG placement. The authors showed that prophylactic PEG improved nutritional parameters and unexpected hospitalization [22]. Esophageal cancer is another indication for EN if patients present symptoms of severe dysphagia and when palliation by placement of an endoscopic stent is not feasible[23]. In general, all oncological diseases that imply hypercatabolism that is not compensated by oral intake may require EN by nasogastric tube or PEG[3].

Other indications

Other indications of PEG that are not for nutritional purposes have also been described. An endoscopic gastrostomy may be placed in patients with gastric outlet obstruction or intestinal strictures that cannot be managed through the usual endoscopic approach, by placement of an endoscopic stent, or creating an endoscopic ultrasound (EUS)-guided gastroentero-anastomoses[24-27]. These conditions can benefit from gastric decompression by PEG[28]. This technique aims to improve the patient's symptoms and reduce GI distension. Primarily, it can be connected to an aspirator to quickly relieve symptoms. Later, it can be connected to a drop bag to improve compliance. This also allows patients to eat small quantities of food in order to guarantee a better quality of life, although some poor nutritional benefits may remain.

In a recent systematic review with 1194 cases, 90% of technique success rate had been reported. However, it showed minor AEs (leak 6.7%; peristomal infections 5.1%; device malfunction 2.8%, and

Table 1 Indications for percutaneous endoscopic gastrostomy placement

Benign	Malignant	Pediatric
Neurological diseases and psychomotor retardation. Cerebrovascular disease. Motor neuron disease (amyotrophic lateral sclerosis). Multiple sclerosis. Parkinson's disease. Dementia. Psychomotor retardation. Reduced level of consciousness. Head injury. Intensive care patients. Prolonged coma. Burns. Short bowel syndromes (Crohn's disease). Facial surgery. Polytrauma. Benign esophageal strictures. Other causes of malnutrition (anorexia)	Cerebral tumor. Cancer with catabolic status. Head and neck cancer. Esophageal cancer. Gastric decompression	Cerebral palsy. Congenital anomaly (*e.g.*, trachea esophageal fistula). Cystic fibrosis. Short bowel syndrome

Table 2 Contraindications to percutaneous endoscopic gastrostomy placement

Relative	Absolute
Peptic ulcer bleeding with high risk of rebleeding. Ascites. Ventriculoperitoneal shunts. Abdominal scars. Large intrathoracic hiatal hernia	Coagulation disorders (INR > 1.5, PTT > 50 s). Platelet count < 50000 mm^3. Sign of sepsis. Peritonitis. Peritoneal carcinomatosis. Lack of a safe tract for percutaneous insertion. History of total gastrectomy

INR: International normalized ratio; PTT: Partial thromboplastin time.

dislodgement 2.1%) in 19.8% of patients and major AEs (2 deaths for sepsis and bleeding) in 1.9% of patients[29]. Moreover, Baron *et al*[30] described the use of a surgical gastrostomy (SG) as access for a duodenoscope in order to perform an endoscopic retrograde cholangiopancreatography[30]. This technique can be used effectively in patients with biliary diseases and previous bariatric Roux-en-Y gastric bypass surgery[31].

A percutaneous intragastric trocar was designed to serve as a trocar for the endoscopist's introduction of rigid laparoscopic instruments in order to better aid endoscopic therapeutic procedures. This device was placed following PEG placement and was successfully used in pigs to perform endoscopic submucosal dissection, full-thickness resections, and intragastric stapling[32]. The PEG could also be used as an access route to perform combined antegrade and retrograde dilations in esophageal strictures that cause complete obstruction and are difficult to dilate with standard endoscopic techniques[18,33,34].

Pediatric indications

PEG is also indicated in the pediatric setting when there is a low nutritional intake, malabsorption, and dysphagia that leads to malnutrition[35]. This procedure is considered safe in a pediatric population weighing less than 6 kg, with complex neurologic disability, congenital heart disease, cancer, or other complex medical comorbidities[36]. Down syndrome is regarded as an indication for PEG placement in the pediatric setting when there is poor nutritional intake[37]. Likewise, cerebral palsy may represent an indication for EN, but substantial evidence to support this indication is scarce[3]. Other indications for PEG placement are congenital malformations, such as congenital heart failure, which can lead to chronic malnutrition[38]. In a pediatric oncological setting, PEG placement results in improvement of body weight, malnutrition, and oncological outcome[39,40].

PRE-EVALUATION AND CONTRAINDICATIONS TO PEG PLACEMENT

All patients must be evaluated carefully prior to undergoing a PEG. A complete visit with medical history, physical examination, and current therapy must be completed[41]. Observational studies showed that a multidisciplinary team can select patients that are suitable for PEG placement[42]. Indeed, a gastroenterologist, a PEG specialist nurse, a dietician, and a speech and language therapist must evaluate the situation on a case-by-case basis. The time of observation of the patient by the nutritional team could require up to 7 d prior to deciding whether the procedure is appropriate or not. This period, defined as the "cooling-off period," is reported as a high-risk phase, where 43% of patients pass away. For this reason, waiting a week could avoid inappropriate procedures in patients with a short life expectancy[43]. However, there are some conditions that represent relative or absolute contraindications for PEG placement. The most common are reported in Table 2.

Recent peptic ulcer bleeding with high risk of rebleeding and hemodynamic and respiratory instability are considered relative contraindications[44]. There are also controversial studies about PEG placement in patients with ascites. In a retrospective study of 29 patients with advanced cirrhosis, Baltz *et al*[45] reported high mortality in patients with ascites who underwent PEG placement. Another case control study evaluated 583 cirrhotic patients, 107 of whom had ascites. It showed no difference in terms of mortality, infections, and bleeding after PEG insertion[46].

Furthermore, particular attention must be paid in patients with ventriculoperitoneal shunts (VPS). In a systematic review, a high incidence of infections and PEG malfunctions were reported (12% and 4%, respectively) in these patients[47]. VPS infections are more frequently reported in cases of PEG placement before the shunt procedure (21.8%) or when a simultaneous PEG and VPS placement were performed (50.0%). For these reasons, the authors of this study suggest performing PEG placement 7-10 d after the VPS. Since many patients that require gastrostomy placement suffer from chronic constipation, which can predispose the transverse colon to move in front of the anterior gastric wall, enemas or a macrogol solution through a nasogastric tube should be given to decompress the colon and reduce the risk of colonic interposition during the endoscopic procedure (Figure 1).

Moreover, anatomical alterations of the abdominal wall (*e.g.*, ostomy, scars, and adhesions) can make PEG insertion difficult. When these conditions are present, PEG placement must be carried out at least 2 cm away from the scar[44]. PEG placement should not be performed in cases of fever, abdominal wall infection, or other signs of sepsis in order to reduce the risk of PEG site infection.

Additionally, PEG placement is considered a high bleeding risk procedure[3,48]. Preprocedural blood tests, with platelet count and coagulation tests, should be done. Indeed, a platelet count < 50000 mm^3 and an international normalized ratio > 1.5 are considered contraindications for PEG placement[48].

Moreover, home antiplatelet and anticoagulant therapy should be evaluated, as all patients are stratified in high or low thrombotic risk. Patients with low thrombotic risk who take antiplatelet (anti-P2Y12) should discontinue the medication 5 d prior to PEG placement. On the other hand, patients with a high thrombotic risk must continue cardioaspirin monotherapy, while other antiplatelet medications are to be assessed by a cardiologist. Traditional anticoagulants should be discontinued 2-5 d prior to the procedure, depending on patient comorbidities and renal function and should be replaced by low molecular weight heparin with an international normalized ratio below 1.5. New anticoagulant should be discontinued 2-3 d prior, based on the different drug subtypes and renal function[48]. However, all antiplatelet and anticoagulant drugs should be resumed 2 d after PEG placement[48].

ENDOSCOPIC *VS* RADIOLOGIC *VS* SURGICAL

Gastrostomy tube placement can be performed by three different techniques: Endoscopic (PEG), radiologic, and surgical[49]. Frequently, PEG is considered the standard procedure, but other techniques are often performed, mainly in patients that are unable to undergo the endoscopic approach[50,51]. Several AEs were reported after all subtypes of gastrostomy placement[52,53]. The most common AEs were device malfunction (52%) and infections (19%)[54]. Some comparative studies on PEG *vs* radiologic gastrostomy (RG) reported results that were univocal. One meta-analysis of 5680 patients reported fewer major AEs in patients undergoing RG than in those undergoing PEG [success rate RG: 99.2% *vs* PEG: 95.7%, $P < 0.001$; major complications RG: 5.9% *vs* PEG: 9.4% *vs* SG: 19.9%, $P < 0.001$][55].

Moreover, another systematic review and meta-analysis evaluated 934 PEG and 1093 RG, indicating that PEG was safer than RG[56]. However, many studies report no statistical differences between these techniques[57,58]. A retrospective study including 184068 patients comparing PEG, RG, and SG was recently published. The authors of this study reported that PEG was safer than RG and SG procedures. In particular, when compared to RG and SG, PEG showed a low rate of infections (RG: 1.28; $P = 0.006$ and SG: 1.61; $P < 0.001$), bleeding [odds ratio (OR) RG: 1.84; $P = 0.002$ and SG: 1.09; $P < 0.001$), perforation (OR RG: 1.90; $P = 0.002$ and SG: 6.65; $P < 0.001$), readmission (OR RG: 1.07; $P = 0.002$ and SG: 1.13; $P = 0.01$), and mortality (OR RG: 1.09; $P = 0.01$ and SG: 1.55; $P < 0.001$)[54]. In conclusion, it is not clear which technique is better among the three mentioned above. Nevertheless, PEG seems to have a lower rate of AEs reported. Moreover, not all hospitals have tools and staff dedicated to performing these procedures. For this reason, it seems reasonable to use the safest method available in the facility.

PEG TECHNIQUES

Different endoscopic techniques for PEG placement have been proposed during the years, including the pull technique, the introducer technique, and the push technique.

Pull technique

The pull technique is the most used procedure for PEG placement[59]. This technique was first described in 1980 by Gauderer *et al*[8]. Two operators are needed: One to manage the endoscopic part of the procedure and one to manage the percutaneous site of the procedure. With the patient placed in the supine position, the abdomen is draped in a sterile fashion, and the gastroscope is inserted perorally into the stomach under conscious sedation or deep sedation. Gastric distension with endoscopic air insufflation brings the anterior gastric wall in contact with the abdominal wall. The lights in the room should be dimmed so that the puncture site can be localized on the abdominal wall by endoscopic transillumination and by clear endoscopic visualization of the indentation of the stomach by external

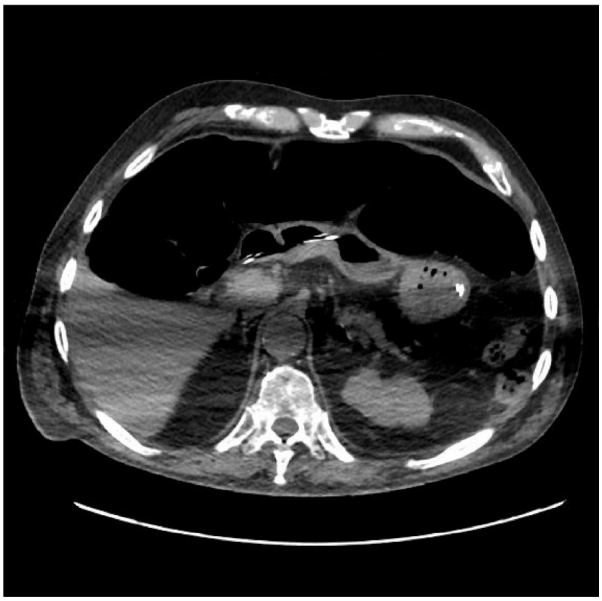

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Figure 1 Case of percutaneous endoscopic gastrostomy failure. Subsequent computed tomography scan showed colonic interposition between the stomach with nasogastric tube and the anterior abdominal wall due to fecal stasis.

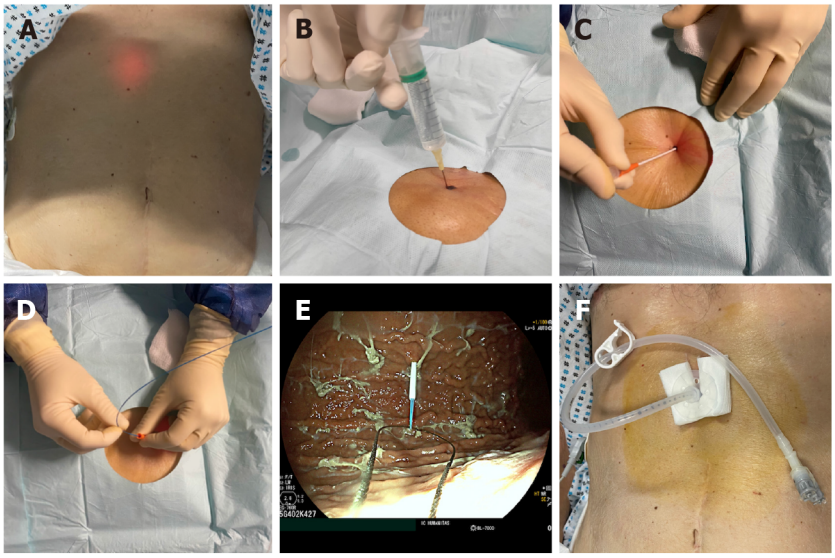

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Figure 2 Steps of percutaneous endoscopic gastrostomy placement with "pull" technique. A: Location of the puncture site *via* transillumination; B: Avoidance of bowel interposition confirmed by the absence of bubbles at aspiration; C: Introduction of the trocar; D: Introduction of the guidewire; E: Grasping the guidewire with an endoscopic snare; F: Final result.

palpation on the marked point.

Then, the "safe track technique"[60] is performed by inserting a 25 G needle attached to a 10 mL syringe that is partially filled with saline solution at the marked point. If bubbles appear in the syringe while aspirating immediately before the needle passes into the stomach, there may be an intervening loop of bowel present. This maneuver could also be performed while withdrawing the needle. Once the puncture site is identified, local anesthesia is given and a skin incision with a surgical blade of 3-5 mm is made so that a 14 G trocar can be inserted under direct endoscopic visualization while keeping constant endoscopic air insufflation of the stomach. Endoscopically a snare, passed through the gastroscope, is looped around the sheath. A dedicated gastrostomy kit wire is then passed through the sheath and into the stomach. It is grasped by the snare and is brought out through the mouth, together with the endoscope.

Thereafter, the gastrostomy kit tube is attached to the wire, and they are pulled back together through the mouth, the esophagus, the stomach, and out through the cutaneous puncture site until the internal

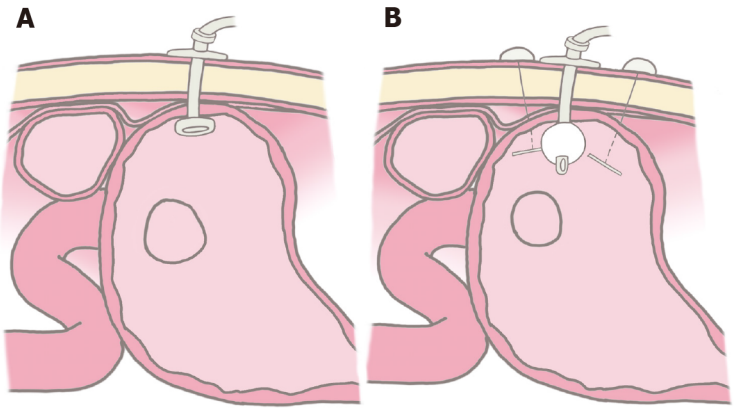

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Figure 3 Graphic representation of percutaneous endoscopic gastrostomy placement technique. A: "Pull" technique; B: "Introducer" technique.

bumper reaches the anterior wall of the stomach. Finally, the external bumper must be fixed against the skin (Figure 2). The described technique can also be done by passing an ultra slim endoscope and the gastrostomy probe transnasally. This variant of the procedure has been described to be well tolerated even in non-sedated patients.

Introducer technique

The direct percutaneous technique, namely the introducer, was first described in 1984 by Russell *et al* [61] and then revised by Brown *et al*[62] in which the stomach is fastened to the abdominal wall with T-fastener sutures. In this technique, two operators are needed, and the gastrostomy site is identified in the same manner as in the "pull" technique. However, while maintaining full gastric endoscopic insufflation, a gastropexy is made by placing two to four T-fasteners circumferentially over the anterior abdominal wall under endoscopic guidance. Within the area between the T-fasteners lies the site for the gastrostomy tube placement[63]. A horizontal incision is made at the identified site so that a trocar can be inserted, and a guidewire introduced into the stomach.

Then, the tract is dilated using dilators that are introduced over the guidewire. Finally, a gastrostomy balloon-type probe is placed over the guidewire through the dilator peel-away sheath and into the stomach (Figure 3). Using this technique, the gastrostomy probe is introduced directly from the exterior through the abdominal wall percutaneously, avoiding contamination of the probe during the passage in the upper digestive tract. This technique should be preferred in patients with esophageal strictures or head and neck cancer to reduce the risk of tumor seeding[3]. In the literature, various cases of gastrostomy site metastasis in patients with upper aerodigestive tract malignancies have been reported, and a recent meta-analysis found that the incidence rate increases particularly in patients with advanced-stage disease[64,65].

Other percutaneous gastrostomy techniques

The "push method" or Sacks-Vine[66] technique is similar to the "pull" method except that the gastrostomy probe is passed over a guidewire from the mouth to the cutaneous side of the gastrostomy. This requires that the tube needs to be much longer and is made of two pieces connected together with a small dilator. EUS-guided PEG placement has also been described[67,68]. In the Baile-Maxía *et al*[67]'s case series, a EUS target was created by filling a sterile glove with saline and was placed over the abdomen of the patient. A linear echoendoscope was passed perorally into the stomach and was positioned against the anterior gastric wall where the EUS target was identified. The abdominal wall was then punctured from inside the stomach with a 19 G needle, and a guidewire was advanced. The guidewire was tied to a string that was passed into the stomach and taken out through the mouth. The following passages are the same of the pull technique. This variation of the pull technique could be selected in obese patients or in patients with previous abdominal surgeries where transillumination could be absent.

AES

Aspiration

This is the most common periprocedural AE[69,70], which has been reported to be around 1%. Risk factors for aspiration are advanced age, need for sedation, and neurologic impairment[71].

Pneumoperitoneum

Transient subclinical pneumoperitoneum is commonly found after the procedure and generally does not have clinical relevance[72].

Injury to adjacent viscera

Under transillumination, if the indentation site is identified and the "safe track technique" is used during the PEG placement, there is a very low risk of injury to the organs adjacent to the anterior abdominal wall, such as colon or liver. If the patient presents severe postprocedural hypotension, liver laceration should be suspected, and urgent computed tomography scan is required. Transhepatic insertion of a gastrostomy tube is a rare and serious AE. Cases reported in the literature have been managed conservatively if the patient remained asymptomatic[73] or surgically if a life-threatening complication such as severe hemorrhage occurred[74]. Colonic injury can present a few days after the procedure, with leakage of the intestinal contents around the gastrostomy tube, abdominal pain, and fever[75]. A computed tomography scan using a hydrosoluble contrast agent should be performed. If no leak into the peritoneal cavity is detected, then the complication can be managed with endoscopic closure of the fistulous tracts[76]. If the patient develops generalized peritonitis, then surgical revision is mandatory. However, in most cases, a gastro-colonic-cutaneous fistula remains clinically silent until months after the gastrostomy placement the first implanted probe is removed, and the replacement tube is placed into the colon (Figure 4). Once nutritional feeding is resumed, diarrhea develops. If a new gastrostomy placement is needed, then laparoscopic gastrostomy should be considered[77,78].

Bleeding

Mild intraprocedural oozing from capillaries could be encountered during the procedure, but they are usually self-limiting or managed with endoscopic therapy. Major bleeding is a rare AE and is usually caused by the puncture of the left gastric or gastroepiploic arteries or one of their branches[79].

Wound infection

The systematic use of prophylactic antibiotic therapy has drastically reduced the incidence of this complication[80]. It generally manifests in redness, edema, and leakage of pus from the gastrostomy site and is usually managed with systemic antibiotic therapy and local wound care (Figure 5). If not treated adequately it can result in necrotizing fasciitis, a rare but potentially fatal complication.

Granulation tissue

Re-epithelialization of gastric mucosa could cause the development of excessive granulation tissue at the gastrostomy site. Treatment consists of avoiding occlusive dressings, and if the mucosa causes persistent minor bleeding, then topical silver nitrate or argon plasma coagulation can be applied to the tissue[81].

Buried bumper syndrome

Buried bumper syndrome is defined by the migration of the internal bumper along the gastrostomy fistula tract. It is generally related to excessive traction from the outside of the internal bumper, which perpetuates over time, leading to a local tissue pressure necrosis and subsequent progressive migration of the internal bumper. To avoid this AE, it is recommended to keep the outer bumper loose from the skin and to periodically check that the gastrostomy tube remains easily rotatable. When the internal bumper has reached the subcutaneous plane, a bulging on the skin is visible at the gastrostomy site, which is hard to the touch, and the gastrostomy tube is not moveable. If, on the other hand, the internal bumper is in the gastric wall, the peristomal skin may appear regular, but the gastrostomy tube will still not be moveable.

Based on the depth of the buried bumper, different extraction techniques can be applied[82,83]. When part of the internal bumper is still endoscopically visible, the buried bumper, after inserting a wire through the gastrostomy tube from the outside, can be effectively pushed back into the stomach with a dilator (*e.g.*, Savary bougie size 15 Fr in 20 Fr gastrostomy tube). Totally or near-totally ingrown bumpers can be removed by cutting the overlying mucosa with an endoscopically guided application of electrosurgical current using a sphincterotome, a needle-knife, or a hook knife. In cases of clear extragastric localization, surgical treatment may be needed.

In a recent study, Costa *et al*[84] reported the use of a novel endoscopic dedicated device, the Flamingo device, for buried bumper syndrome management. The Flamingo device is inserted over the guidewire into the stomach through the external insertion of a partially cut gastrostomy probe. The distal part of the Flamingo device is flexed to 180° using its dedicated handle, exposing the bowstring, sphincterotome-like cutting wire. External traction is then applied to the Flamingo device from the cutaneous side of the gastrostomy, pulling the flexed cutting wire toward the granulomatous tissue through direct endoscopic visualization until apposition is achieved, and the overgrown tissue is then incised.

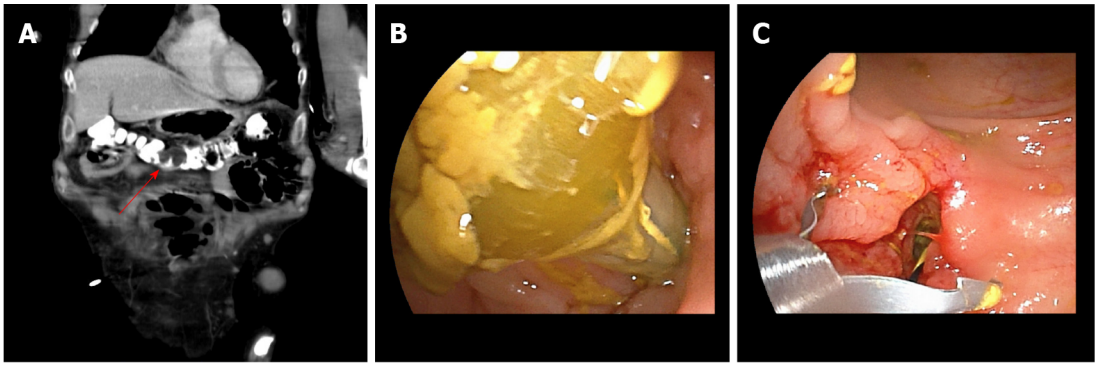

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Figure 4 Percutaneous endoscopic gastrostomy displacement and development of colocutaneous fistula. A: Computed tomography scan image showing percutaneous endoscopic gastrostomy balloon located in the transverse colon (red arrow); B: Endoscopic view of the percutaneous endoscopic gastrostomy balloon within the colon; C: Endoscopic closure of the colonic fistulous orifice with clips.

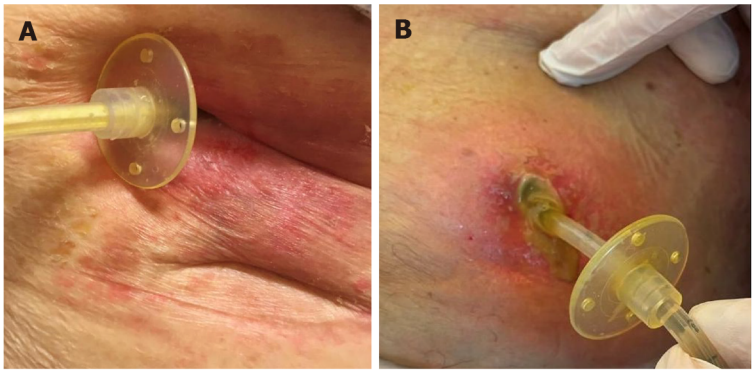

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Figure 5 Wound infections. A: Superficial infection of the abdominal wall; B: Wound infection with abscess formation within the anterior abdominal wall.

Tube displacement

If probe removal occurs earlier than 4 wk after the gastrostomy placement, the fistula may not have consolidated. Therefore, a percutaneous replacement should not be attempted. After the probe removal, the patient must be placed under broad antibiotic coverage and must fast for at least 24 h. The placement of a new endoscopic gastrostomy should be scheduled after complete wound healing. In the case of a probe removal after 4 wk, the attempt to percutaneously place a replacement probe is indicated and should be done quickly because in the absence of a tube in the gastrostomy tract, the gastrocutaneous fistula tends to close spontaneously within 12-24 h[85]. Our advice is that if a replacement probe is not available at the time of displacement, another tube (*e.g.*, 18-20 Fr Foley catheter) should be placed temporarily as soon as possible in order to avoid the risk of closure of the fistulous tract.

Peristomal leakage of gastric content

This is generally linked to a patient's clinical condition that led to a delayed gastric emptying, which may be due to either pre-existing conditions such as gastroparesis or to the presence of fecal impacts that alter intestinal transit leading to sub-occlusive symptoms. It can be managed by trying to improve gastric emptying with the use of prokinetics in order to reduce gastric secretions with the use of protein-protein interactions and to improve intestinal canalization with the periodic administration of macrogol through the gastrostomy tube. Local skin irritation can be prevented by stoma adhesive powder or zinc oxide application. When the condition does not resolve with the optimization of medical therapy, the positioning of a jejunal extension is indicated to prevent the feeding solution remaining in the stomach and for the gastric tube to be used as a drainage of gastric secretions to progressively reduce the peristomal leakage.

Gastrocutaneous fistula

Once the probe has been removed, the gastrostomy usually closes within 12-24 h. The nonclosure of the fistula is often caused by severe malnutrition and a reduced thickness of the fistulous tract. If the external bumper is positioned too close to the skin, the continuous compression of the skin leads to tissue ischemia with reduction of the thickness of the fistulous tract. When the thickness of the fistulous

tract is 1-2 mm, the closure of the fistula by a secondary intervention becomes very difficult and it is often necessary to perform an endoscopic closure, using techniques similarly to GI perforation[86-90] (Figure 6).

POST-PROCEDURAL CONSIDERATIONS

At the gastrostomy site, the PEG tube can be used for infusion after 12-24 h of placement. To start, begin with water followed by regular EN with progressive increase in the infusion rate. In the first 72 h, the external bumper must be fixed against the skin to allow adequate attachment of the abdominal wall to the gastric wall, which is fundamental for a correct maturation of the fistula. After 72 h the external bumper should be detached from the skin by at least 0.5-1.5 cm to avoid compression of the skin as the patient's position changes. This compression would increase the risk of developing subcutaneous infections and, in the long term, would lead to ischemia of the wall itself, with a progressive reduction in the thickness of the fistula wall. At least 4 wk after the PEG creation, the gastrocutaneous fistula is considered to be fully consolidated. In very undernourished patients, the maturation of the fistula may take longer. The peristomal skin should be kept clean daily by using only mild soap and water, and the gastrostomy site should be left open without occlusive dressings, which may lead to peristomal skin maceration.

Enteral tube replacement

There are no exact evidence-based guidelines regarding the replacement of PEG tubes. Therefore, each center adopts its own protocol based on the management of these patients, which is very complex because they are generally very fragile and undernourished and may have neurological diseases that compromise their autonomy. We can certainly distinguish the timing of replacement of the first implanted probe based on the probe material[91]. There are probes, generally those that can only be removed perorally, that are manufactured using resistant materials and remain functional even after 1 year or 2 years. On the other hand, there are probes which can be removed percutaneously using traction, which are made of more flexible materials. However, these tend to wear out more quickly over time. The deterioration of the probe becomes evident externally, which then corresponds to the deterioration of the internal bumper and becomes more rigid, compromising the flexibility necessary for removal by percutaneous traction. Therefore, the removable traction probes should be removed usually about 6 mo after placement at bedside without endoscopic control.

However, when the attempt of removal of this type of tube is made after many months, the percutaneous traction removal becomes more and more difficult, requiring a different approach. In this situation, the probe is removed by cutting the tube from the external skin margin and the internal bumper is left in the stomach. Endoscopic retrieval of the bumper in the stomach is recommended in patients at risk of intestinal occlusion[3]. The balloon-type gastrostomy probes[92], which are applied during the procedure of direct percutaneous gastrostomy and are used as replacement after removal of the first implanted probes, have a balloon as an internal bumper. This balloon, after the percutaneous insertion of the tube and when the gastric cavity is reached, is filled with sterile water. The advantage of a balloon-type probe is that it can be easily removed by just deflating the internal balloon. The disadvantages are that they tend to wear out quite quickly over time and that they can be easily removed accidentally. The substitution of this type of probe should be made every 3-6 mo.

Follow-up of patients with a gastrostomy tube

The management of patients after gastrostomy placement varies according to local protocols. It is generally a multidisciplinary management that involves home care nursing, nutritional planning, and specialized medical support. Training courses are held for the relatives of the patients who will play a fundamental role in caring for these patients. The balloon type tubes can be easily replaced at home by dedicated staff with a low risk of AEs[93]. The home management of these patients is essential because they are very fragile and, in most cases, not mobile or independent. Therefore, staying in the hospital is risky and difficult to manage[94].

PEG WITH JEJUNAL EXTENSION

Percutaneous endoscopic transgastric jejunostomy (PEG-J) is a gastrostomy with a jejunal extension tube. The jejunal extension tube can be positioned "beneath the scope," grasped endoscopically with forceps in the stomach lumen, and dragged into the jejunum or "over the wire" that is advanced over an endoscopically or radiologically placed guidewire. The placement of the jejunal extension tube should be attempted in patients with gastrostomy feeding-related AEs, such as aspiration pneumonia due to gastroesophageal reflux of the gastric feed and uncontrolled peristomal leakage[9]. The feeding solution can be administered from the jejunal extension tube, and the gastric tube can perform the gastric

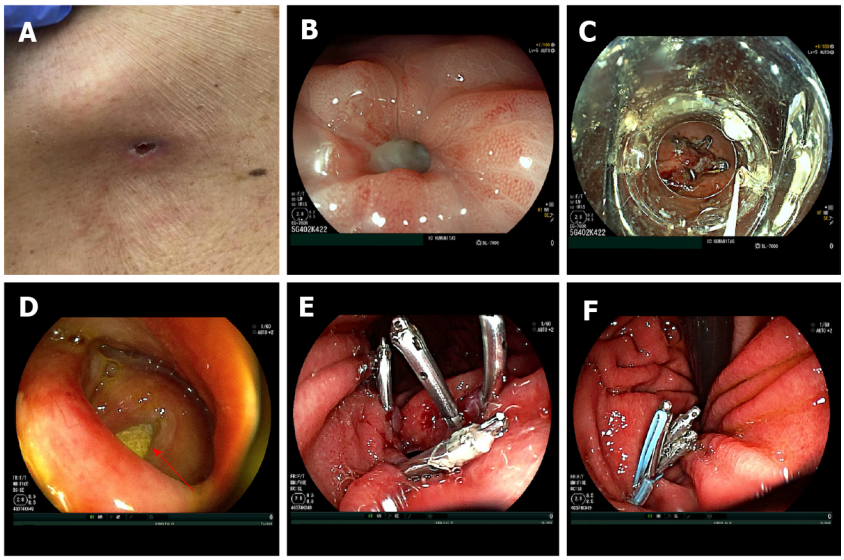

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Figure 6 Gastrocutaneous fistula. A: External appearance of a gastrocutaneous fistula in the first case; B: Endoscopic appearance of the gastrocutaneous fistulous orifice; C: Endoscopic closure of the gastric fistulous orifice with an over-the-scope metal clip in the first case (OTSC – Ovesco Endoscopy AG, Tubingen, Germany); D: Endoscopic appearance of a large gastrocutaneous fistula, with detection of the gauze placed from the outside at the cutaneous end of the tract (red arrow) in the second case; E: Endoscopic placement of four metal clips at the margins of the fistulous orifice; F: Placement of an endoloop over the metal clips to achieve complete closure of the fistulous orifice.

decompression function. PEG-J is also used in Parkinson's disease patients for delivering the levodopa-carbidopa intestinal gel[95]. In this case, the jejunal extension tube allows a continuous delivery of the drug into the small bowel[95] (Figure 7). The disadvantages of these probes are that the jejunal extension tubes are usually long (median length of 55 cm) and small in diameter (median diameter of 9-10 Fr) and are more prone to occlusion, kinking, or dislocation[96]. These tubes also have limited longevity and tend to wear out after 3-6 mo, especially if they are used as EN feeding devices.

DIRECT PEJ

Direct PEJ (DPEJ), described in 1996 by Shike *et al*[97], is an alternative method of EN feeding in patients that cannot undergo gastrostomy placement because of previous resection of the esophagus or stomach, or in patients with frequent clogging or migration of PEG-J extension. In these circumstances, DPEJ placement is performed using the same passages of the gastrostomy technique. Likewise, this technique is needed to achieve the proximal or medium jejunum under endoscopic visualization by a push enteroscopy, single-balloon or double-balloon enteroscopy, or underwater enteroscopy[98]. The use of ultrasonography, fluoroscopy, or anchoring a needle to the jejunum can be used to facilitate correct placement. Jejunal probes placed through DPEJ are shorter and greater in diameter compared to jejunal tubes placed through PEG-J, making them less prone to tube dysfunction.

However, DPEJ is a challenging technique with a successful placement between 68% and 83%, which is highly variable based on local expertise. Endoscopic access up to the jejunum is not straightforward, and once obtained, the major difficulty is to identify the target jejunal puncture site. Serious periprocedural AEs have been reported, such as bowel perforation (up to 2.5%) and volvulus. A frequently reported post-procedure AE is peristomal leakage with fistula enlargement, which is aggravated by leakage of pancreatic juice and bile causing peristomal irritation and severe dermatitis[99,100]. DPEJ is a useful technique in order to avoid the need for surgery when long-term nutritional jejunal access is needed. However, it is associated with a moderate or severe complication risk in up to about 10% of the cases, which physicians should be aware of (Figure 8).

FUTURE PERSPECTIVES

The data within this paper confirms that PEG placement is a safe procedure. The selection of patients requiring PEG will be of paramount importance to understanding which individuals may benefit more from this nutritional support than others, maximizing the outcomes, and reducing the AEs. Considering the complexity of these patients, a dedicated multidisciplinary team for pre- and post-procedural management are required for patient care. Moreover, the development of a home health care service for

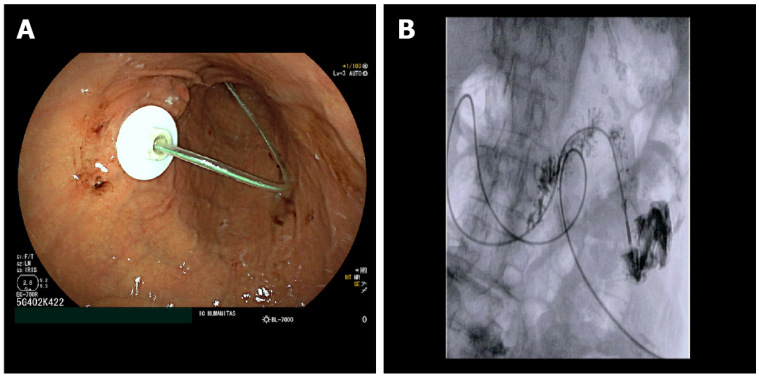

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Figure 7 Percutaneous endoscopic transgastric jejunostomy placement. A: Endoscopic appearance of the percutaneous endoscopic transgastric jejunostomy with jejunal extension entering from the percutaneous endoscopic transgastric device towards the jejunum; B: Final fluoroscopic appearance of the percutaneous endoscopic transgastric jejunostomy with distal end of the jejunal extension into the proximal jejunum after injection of contrast medium.

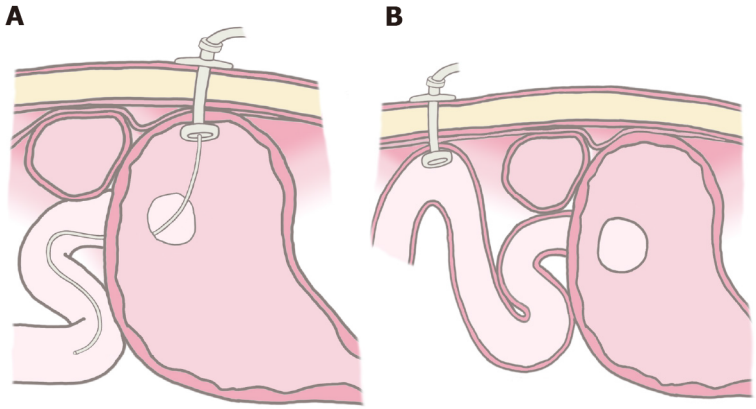

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Figure 8 Graphic representation. A: Percutaneous endoscopic gastrostomy with jejunal extension; B: Direct percutaneous endoscopic jejunostomy.

nutrition support and device management, consisting of a gastroenterologist, nurse, and nutritionist is fundamental to avoid patient transportation. In particular, the coronavirus disease 2019 outbreak has significantly impacted our clinical practice, and we have established infection prevention measures in order to protect both patients and personnel[101-104]. Moreover, the pandemic definitively underlined the importance to reduce hospital visits, especially for such fragile patients[27]. Currently, the main purpose of PEG placement is for nutritional support. However, other ingenious gastrostomy-related procedures have been described in the literature that are not for nutritional purposes, including gastric decompression in GI malignancies, access for endoscopic retrograde cholangiopancreatography in patient with surgically altered anatomy, and access of the trocar for therapeutic procedures. The introduction of dedicated devices into clinical practice for therapeutic procedures through a PEG will expand the possible indication for PEG placement.

CONCLUSION

PEG is a safe and effective procedure even if performed in fragile patients. The selection of patients and the creation of a dedicated team for pre- and post-procedural care is fundamental to obtain good outcomes and reduce AEs. Moreover, careful selection of the best approach used over the different endoscopic approaches is required. Finally, the stoma can be used not only for nutritional purposes but also as an access route for advanced endoscopic procedures.

FOOTNOTES

Author contributions: Fugazza A, Capogreco A, and Cappello A drafted the manuscript; Rosangela Nicoletti R, Da Rio L, Galtieri PA, Maselli R, Carrara S, Pellegatta G, Spadaccini M, Vespa E, Colombo M, and Khalaf K contributed

to the acquisition, analysis, or interpretation of data for the work; Repici A and Anderloni A contributed to the critical revision of the manuscript; All authors approved the final version to be published.

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REVIEW

Current updates and future directions in diagnosis and management of gastroenteropancreatic neuroendocrine neoplasms

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Abstract

Gastroenteropancreatic neuroendocrine neoplasms are a heterogenous group of rare neoplasms that are increasingly being discovered, often incidentally, throughout the gastrointestinal tract with varying degrees of activity and malignant potential. Confusing nomenclature has added to the complexity of managing these lesions. The term carcinoid tumor and embryonic classification have been replaced with gastroenteropancreatic neuroendocrine neoplasm, which includes gastrointestinal neuroendocrine and pancreatic neuroendocrine neoplasms. A comprehensive multidisciplinary approach is important for clinicians to diagnose, stage and manage these lesions. While histological diagnosis is the gold standard, recent advancements in endoscopy, conventional imaging, functional imaging, and serum biomarkers complement histology for tailoring specific treatment options. In light of developing technology, our review sets out to characterize diagnostic and therapeutic advancements for managing gastroenteropancreatic neuroendocrine tumors, including innovations in radiolabeled peptide imaging, circulating biomarkers, and endoscopic treatment approaches adapted to different locations throughout the gastrointestinal system.

Key Words: Gastroenteropancreatic neuroendocrine neoplasms; Neuroendocrine tumors; Neuroendocrine carcinoma; Gastrointestinal; Pancreas; Small intestine

Core Tip: Diagnostic technology for neuroendocrine tumors continues to advance. Radiomics promises to enhance morphologic imaging. Gallium-68 DOTA-peptide positron emission tomography/computed tomography has replaced Octreoscan as the preferred functional imaging modality. Newer radiolabeled peptides may further improve detection. A novel liquid biopsy biomarker (NETest) has proven more accurate than chromogranin A in monitoring treatment response and predicting disease activity. Therapy has also progressed with treatment adapted based on the predicted behavior of the tumor. Advanced endoscopic resection techniques have revolutionized treatment. Preliminary evidence suggests endoscopic ultrasound guided radiofrequency ablation may prove useful in treating pancreatic lesions. Multimodality therapy continues to evolve for metastatic pancreatic tumors.

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INTRODUCTION

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a heterogenous group of rare neoplasms with a wide clinicopathologic spectrum of disease activity[1]. These neoplasms arise from the secretory cells of the neuroendocrine system and can occur anywhere along the gastrointestinal tract[2]. Nearly 95% occur sporadically, though genetic testing should be considered for patients less than 40 years old, family history of NENs, features concerning for multiple endocrine neoplasia type 1, von Hippel-Lindau disease, tuberous sclerosis or neurofibromatosis type 1[3]. Traditional terminology including carcinoid tumor and APUDoma were replaced by neuroendocrine neoplasm in 2010 by the World Health Organization (WHO), which also discouraged using the terms benign and malignant. NENs are grouped as well-differentiated neuroendocrine tumors (NET) or poorly differentiated neuroendocrine carcinomas (NEC)[4]. NECs are highly aggressive with significantly worse prognosis. Nearly 80%-90% of GEP-NENs are NETs, which are slow growing and graded from G1 (low), G2 (intermediate), to G3 (high)[2].

With the advent of high-resolution cross-sectional imaging, GEP-NENs are increasingly being discovered-notably without any significant change in rates of metastasis[5]. In a large population-based study of 64971 patients, the age-adjusted incidence rate of NETs increased from 1.09 per 100000 in 1973 to 6.98 per 100000 in 2012, with the greatest increase occurring in localized NETs and G1 NETs[6]. These observations suggest that many of these lesions are incidental and/or asymptomatic at the time of discovery. Incidence of gastric and rectal NETs has increased the greatest unlike small bowel NETs, which likely correlates with greater use of endoscopic procedures. Similar trends have been noted in Europe and Asia[7].

GEP-NENs are divided into gastrointestinal and pancreatic NENs with the most common being rectal (29%) and small intestinal (28%) (Figures 1 and 2)[8,9]. These tumors exhibit a wide range of behavior with varying degrees of disease activity including growth rate, grade, differentiation and metastatic potential[10]. Generally speaking, small intestinal NENs have high malignant potential while gastric, duodenal, appendiceal, and rectal NETs are less likely to metastasize[11]. A recent cohort of 43751 patients in the United States noted that the majority of GEP-NENs were localized (51.7%) and grade 1 (71.7%)[9]. This study also found that the most lesions (73%) occurred in whites, followed by black (16.2%) and Asian (7.3%) populations with no difference in three or five year survival based on race.

The majority of GEP-NENs are non-functional while functional NENs secrete hormones and substances that lead to clinical symptoms. Functioning gastrointestinal NENs are not classified separately from nonfunctioning gastrointestinal NENs and manifest with carcinoid syndrome while functioning pancreatic NENs are classified distinctly according to the hormone secreted by the tumor. Nonhormonal products are also produced by both non-functional and functional NENs, which include chromogranin A, pancreastatin and pancreatic polypeptide, and may offer aid in diagnosis and follow-up.

DIAGNOSIS

Diagnosis relies on morphological imaging, functional imaging, endoscopic procedures, biomarkers, and pathology. All patients should undergo computed tomography (CT) and/or magnetic resonance imaging (MRI). Functional imaging serves as an adjunct to conventional imaging in advanced NETs and is helpful for identifying primary tumors and staging. Endoscopic procedure with biopsy diagnoses gastric, duodenal and colorectal NENs while endoscopic ultrasound (EUS) aids in identification of

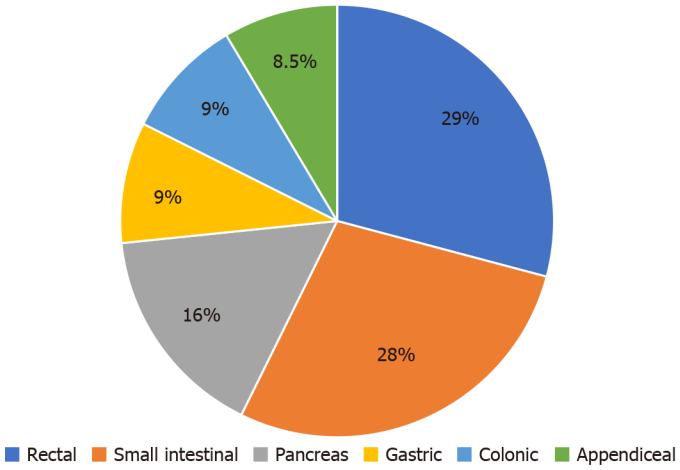

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Figure 1 Epidemiology of gastroenteropancreatic neuroendocrine neoplasms.

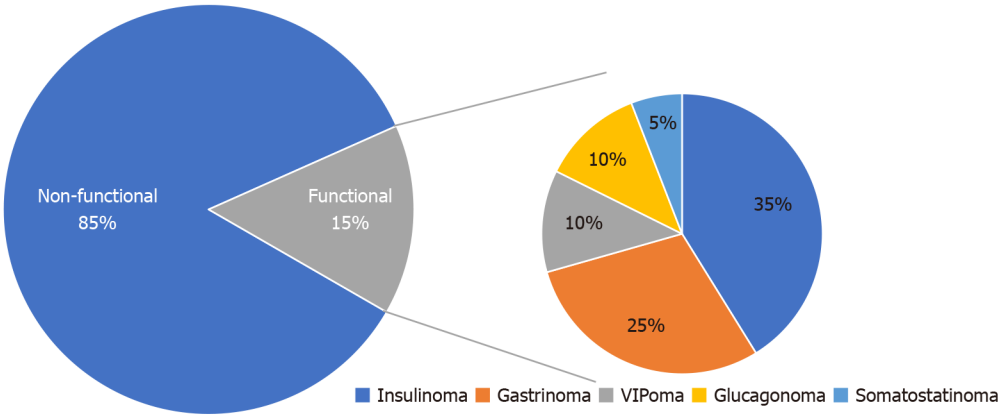

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Figure 2 Epidemiology of pancreatic neuroendocrine neoplasms.

pancreatic NENs. The mainstay of biomarkers is chromogranin A although newer markers have been identified, which may expand the role of biomarkers in post-treatment surveillance and detection of recurrence.

Pathology (staging and grading)

Tumor staging and grading are essential to assess prognosis and disease activity as reflected in the 2019 WHO classification based on tumor differentiation and grading (mitotic rate or Ki-67 index) (Table 1)[2, 4]. The degree of differentiation is based on the extent the tumor cells resemble their endocrine cell counterparts[11]. Grading is based on the proliferative rate from either mitotic counts or Ki-67 labeling index with higher values associated with more aggressive behavior, independent of stage[2]. Mitotic counts rely on the number of mitotic figures in 10 consecutive high-power fields while Ki-67 Labeling index is the percent of positive tumor cells. Small biopsy samples and heterogeneity within the tumor all pose challenges to accurate assessment of tumor grade of the entire lesion. Whether there is incremental benefit from larger core samples obtained during EUS-fine needle biopsy and whether artificial intelligence technology will help partially automate calculating Ki-67 index require further study[12]. Radiomics may supplant or supplement histologic diagnosis by assessing the whole lesion and will be discussed further below.

Morphologic imaging

NETs typically are highly vascular, hyperenhancing in the early arterial phase with washout during the delay portal venous phase of CT (Figure 3). Differentiating liver metastases from hepatocellular carcinomas may be aided by exploiting the fact that hepatocellular carcinomas have higher attenuation levels with contrast and higher iodine uptake with a threshold value of 0.22 for normalized iodine uptake having 100% sensitivity and 90% specificity[13]. Attenuation assessment of lymph nodes on CT

Table 1 World Health Organization 2019 Classification

Terminology, grade	Differentiation	Mitotic count (HPF²)	Ki-67 index (%)
NET, G1	Well-differentiated	< 2/10	< 3
NET, G2	Well-differentiated	2-20/10	3-20
NET, G3	Well-differentiated	> 20/10	> 20
NEC, G3 (small or large cell type)	Poorly differentiated	> 20/10	> 20

NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; HPF: High powered field.

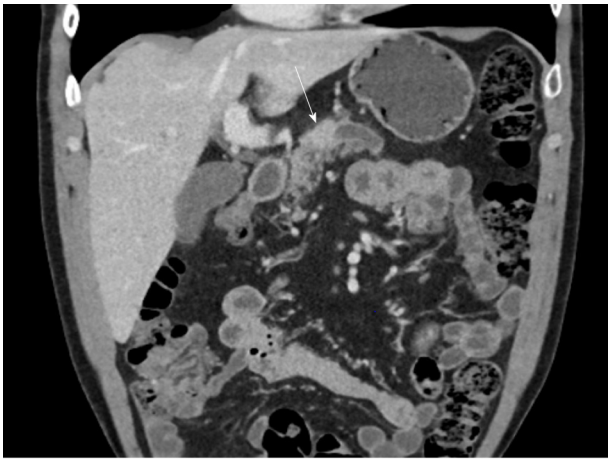

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Figure 3 Computerized tomography scan of hyperenhancing pancreatic neuroendocrine tumor (white arrow).

may also help identify malignant nodes with a cutoff value of 7.5 Hounsfield units distinguishing 96% of positron emission tomography (PET) positive and 89% of PET negative lymph nodes[14]. Limitations of CT include lower sensitivity with a recent study suggesting only 76% of CT scans identified the primary tumor in patients with metastatic GEP-NETs, and difficulties with identifying small (< 1 cm) lesions especially in the small bowel where only 21% of small intestine NETs were identified in one study[15-17]. CT enteroclysis has been used for localization of small bowel tumors[18] with luminal distension using neutral contrast aiding in defining small mucosal features with a positive predictive value of 95%[18].

MRI with contrast enhancement is superior in detecting lesions in the liver and pancreas[15]. With higher tissue resolution, MRI is also better for evaluating bone and liver metastases[19,20]. NENs typically have low T1 and high T2 signal on imaging (Figure 4). Adding diffusion weighted MRI to standard MRI imaging increased metastatic findings in 71% of patients, which changed patient management in 19% of patients[21]. A comparative study showed that while contrast enhanced MRI is superior, adding diffusion weighted to non-contrast MRI imaging may suffice for everyday practice[22].

Radiomics appears to augment the ability of MRI to differentiate pancreatic NET from adenocarcinoma and solid pseudopapillary neoplasms[23,24].

Grading pancreatic NETs by CT or MRI is challenging and relies on assessing tumor margins, pattern of venous phase contrast washout, and enhancement pattern[10,18]. Irregular margins on CT have 71% sensitivity and 82% specificity for predicting grade 2/3 tumors while a model incorporating margins and fusion signature had 0.90 AUC for differentiating grade 1 from grade 2/3 tumors. Tumor texture analysis of CT and MRI images suggests entropy may be most useful in differentiating the different grades with 91% sensitivity and 85% specificity for distinguishing grade 1/2 NET from grade 3 NEC on CT and 83% sensitivity and 61% specificity for separating G2/3 from G1 tumors on MRI[25,26]. Whole tumor apparent diffusion coefficient histogram analysis may help predict the aggressiveness of pancreatic NET with kurtosis being the most useful marker[26]. While exciting, further studies are needed to understand the capabilities and role of radiomics in diagnosing, grading, and potentially prognosticating and guiding treatment.

Functional imaging

Somatostatin receptor imaging provides whole body imaging for NETs based on the wide expression of somatostatin receptors in most well-differentiated NETs. Nearly 70%-90% of gastrointestinal NETs and

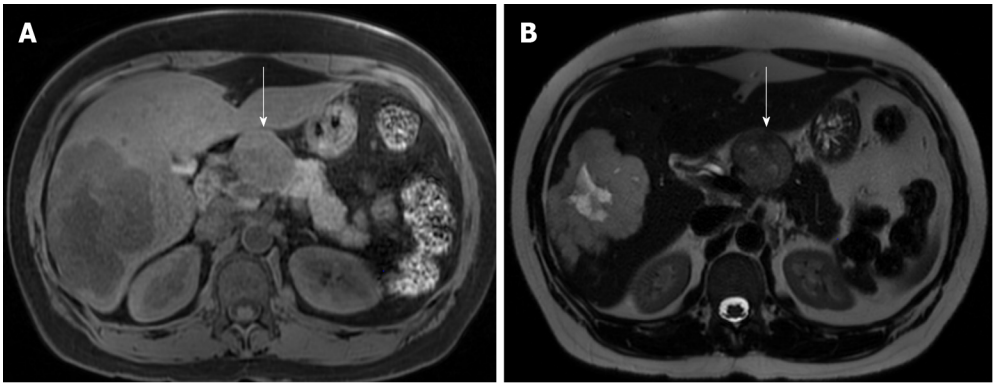

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Figure 4 Magnetic resonance imaging with T1 hypointense and T2 mildly hyperintense well-defined peri-pancreatic neuroendocrine tumor. A: T1 hypointense; B: T2 mildly hyperintense.

50%-70% of pancreatic NETs express somatostatin receptors[27]. Quantification of somatostatin receptor expression can diagnose, stage, and assess response to therapy with somatostatin analogues (SSAs) or peptide receptor radionuclide therapy (PRRT)[15]. Gallium (Ga)-68 DOTA-peptides with PET/CT have replaced traditional Octreoscan [octreotide single-photon emission computed tomography (SPECT)/CT or 111-Inpentetreotide with SPECT] as the preferred modality due to its higher accuracy and shortened procedure time, which reduces radiation exposure (Figure 5)[28]. The sensitivity and specificity to detect NET is 92% and 95%, respectively[29]. Of note, there are different labeled peptides that can be used (DOTA-TOC, DOTA-NOC, and DOTA-TATE), but they are regarded as equally efficient[30]. One meta-analysis of 1561 patients found that using 68-DOTATATE changed management in one third of patients who previously had an Octreoscan[31]. Another study of 101 patients with well/moderately differentiated NETs showed that 68-DOTATATE imaging altered management in 36 patients, which included avoiding the need for biopsy (n = 4), initiating systemic therapy (n = 14), and altering operative plans in half of patients referred to surgery (n = 14)[32]. When available, this modality is preferred due to its high sensitivity and ability to influence management strategies in more than 70% of cases[33,34].

However, it should be noted that the accuracy of Ga-DOTA-peptides PET-CT imaging declines as NET tumor grading increases due to decrease in somatostatin receptor expression[15]. As NETs lose somatostatin receptors, their cells increase glucose utilization[35]. In this context, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT may be the preferred method for identifying high grade lesions. In a large study with 104 biopsy proven NETs where both Ga-DOTATATE and ^{18}F-FDG PET/CT were performed, ^{18}F-FDG PET/CT was most useful in changing management of G3 tumors while not helpful for G1 tumors[36]. Therefore, these authors suggested only limited use of ^{18}F-FDG PET/CT for tumors with Ki-67 ≤ 12%. Ga-DOTATATE and ^{18}F-FDG PET/CT may be complementary imaging modalities. Other studies have suggested this as well with FDG PET-CT being 100% sensitive for identifying poorly differentiated G3 tumors while Ga-DOTATATE had 83% sensitivity for well-differentiated G2/3 tumors[37]. A retrospective study of pathology-proven NENs demonstrated increased sensitivity (94%) for diagnosing NENs when both tracers were used compared to either alone (Ga-DOTATATE 63.8% and ^{18}F-FDG 74.7%)[37]. Ki-67 index also negatively correlated with Ga-DOTATATE while positively correlated with ^{18}F-FDG. Another group developed a NETPET grade from 0 to 5: P0 is negative for both ^{18}F-FDG and 68Ga-DOTA-peptide scans, P1 is 68Ga-DOTA scan positive and ^{18}F-FDG negative, P2-4 are positive for both with varying intensity of uptake, P5 is ^{18}F-FDG positive and 68Ga-DOTA scan negative. This grading system correlated with tumor grade and survival with P5 having lowest median overall survival (11 mo)[38]. NETPET may allow selection of patients for PRRT which relies on the presence of somatostatin receptors to uptake therapeutic radionuclide into the NET cells. Patients with significant ^{18}F-FDG positivity and 68Ga-DOTA negative disease may not respond well to PRRT alone and likely would benefit greater from systemic chemotherapy.

64Cu-DOTA is a new tracer with longer half-life and potentially superior spatial resolution compared to 68Ga[39]. The longer half-life (12.7 h *vs* 1.1 h) would potentially allow 64Cu-DOTA to be used more routinely and readily compared with 68Ga-DOTA. In 59 patients who underwent both 64Cu-DOTATATE and 68Ga-DOTATOC PET/CT, more patients had more lesions detected using 64Cu-DOTA than with 68Ga-DOTA (13 *vs* 3, respectively, P = 0.013)[40]. A phase III US study confirmed the safety and high accuracy of 64Cu-DOTA PET/CT[41].

^{18}F (fluoro-dihydroxyphenylalanine)-DOPA is another radiopharmaceutical that has high sensitivity of 97% and specificity of 90% for small intestinal NETs, and alters management in 50% of small intestinal NETs[42]. In a comparative prospective study, ^{18}F-DOPA outperformed combined CT and somatostatin-receptor scintigraphy imaging in localizing low grade small intestinal NETs[43]. However, other studies have suggested 68Ga-DOTA is superior to ^{18}F-DOPA for detecting well-differentiated

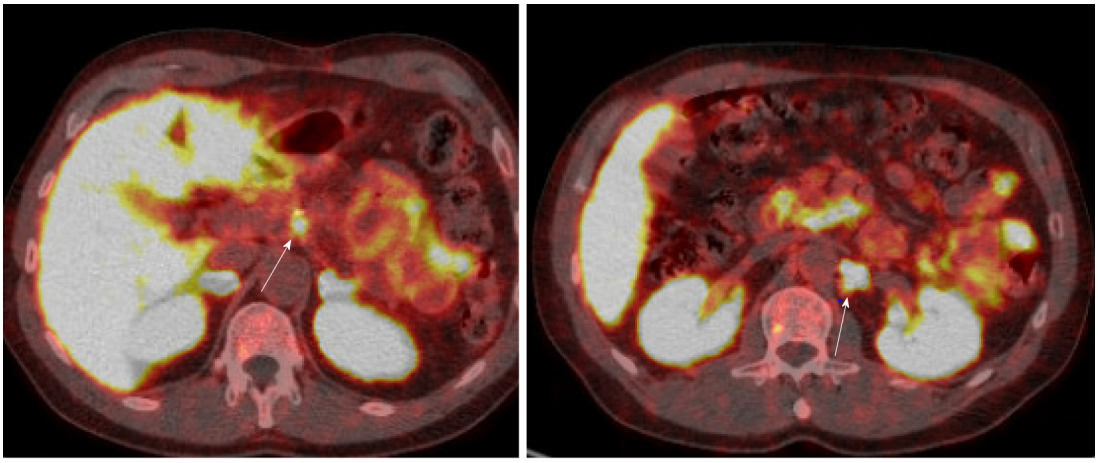

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Figure 5 Gallium-68 DOTATATE positron emission tomography/computed tomography demonstrating avid lymph nodes.

NETs, including small intestinal NETs. ^{18}F-DOPA is not readily available in Western countries, but may be complementary in the evaluation of small intestinal NETs[39,44].

Insulinomas are notoriously difficult to detect using morphological and somatostatin receptor imaging. Because they over-express glucagon-like peptide-1-receptors (GLP-1R), these offer targets for PET-based imaging[39]. 68Ga-DOTA-exendin-4 is a PET agent targeting GLP-1R. In a prospective randomized crossover study of 52 patients with suspected insulinoma, patients underwent 68Ga-DOTA-exendin-4 PET/CT, SPECT/CT and MRI with 68Ga-DOTA-exendin-4 imaging being more accurate than MRI for detecting insulinomas (93.9% and 67.6%, respectively)[45].

There is little literature on the value of PET-MRI, however, one small study demonstrated comparable image quality between 68Ga-DOTA-TOC PET/CT with PET/MRI while another suggested more lesions were identified with PET/MRI[46,47]. Advantages of PET/MRI include use in patients with renal insufficiency and better detection of liver lesions.

Biomarkers

Functional NETs secrete hormones that lead to various clinical symptoms and syndromes. These hormone levels should only be checked in patients with clinical symptoms and syndromes suggestive of a functional NET. Hormone levels may be followed in patients with functional pancreatic NETs to monitor response to treatment and recurrence[48].

Carcinoid syndrome may occur with metastatic NETs, typically from the small intestine. Twenty four hours measurement of urinary 5-hydroxyindoleacetic acid (5-HIAA), an end product of serotonin metabolism, has a specificity and sensitivity of over 90%[49]. Patients should avoid tryptophan-rich foods and certain medications for several days before urine collection. Urinary 5-HIAA may also help predict patients at risk for carcinoid heart disease and carcinoid crisis during surgery as well as those who may respond to SSAs and PRRT[50]. If urine collection is difficult, plasma testing may be more convenient. Compared to urinary measurements, plasma 5-HIAA has a sensitivity and specificity of 89% and 97%, respectively, in diagnosing carcinoid patients[51]. Its widespread use is limited by institutional preferences and lack of validation in clinical studies.

Nonhormonal secretory products are also produced by both functional and nonfunctional NETs and can serve as biomarkers. Chromogranin A, a nonhormonal serum glycoprotein, is the main biochemical marker. However, its use has been deemphasized with the National Comprehensive Cancer Network and North American Neuroendocrine Tumor Society (NANET) not recommending its routine use due to limitations in accuracy, lack of standardization across laboratories (differing assays and isoforms), and unclear added value beyond imaging findings[48,52,53]. It should be measured fasting and at least 2 wk after discontinuation of proton pump inhibitors[54]. Sensitivity is lower in localized disease[55], and chromogranin A levels may drop with use of SSAs due to decreased production of hormones from cells rather than reduction in tumor burden[56].

Consequently, other biomarkers have been investigated. Genetic mutations in DAXX and ATRX expression (which interact with centromeric and telomeric regions) have recently been associated with well-differentiated NENs and poor survival in pancreatic NETs[57]. DNA hypermethylation has been associated with worse prognosis in pancreatic NETs. There is also interest in a new biomarker that measures cell-free DNA which circulates in the plasma following apoptosis, necrosis or active secretion, whereby it may have the potential to differentiate metastatic *vs* localized pancreatic NETs[57,58].

A novel liquid biopsy biomarker (NETest) measures 51 different RNA transcripts relevant to NET using quantitative real-time polymerase chain reaction[59]. Scores range from 0%-100% with 0-20 normal, 4-80 intermediate and ≥ 80 high activity. NETest has recently been reported with favorable

results compared to chromogranin A for monitoring treatment response following both surgery and PRRT[60,61]. In a cohort of 253 GEP-NENs, NETest out performed chromogranin A in terms of accuracy (99% *vs* 53%) and also proved reliable in correlating the grade, stage and progression of GEP-NENs[62]. Another prospective study confirmed high diagnostic accuracy (91%) of NETest, ability to differentiate metastatic from local disease, 91% concordance with CT/MRI/ Ga 68-DOTA peptide PET, correlation with curative *vs* palliative surgeries, and higher diagnostic accuracy compared with chromogranin A [63]. NETest predicted postoperative recurrence at postop day 30 with 94% accuracy while chromogranin A was not helpful[64]. No patients with R0 resection and normal NETest developed recurrence while all R1/R2 patients had elevated NETest. This would allow early identification of patients with residual disease postoperatively who need to be followed more intensely while those with R0 resection and normal NETest likely can have fewer follow-up imaging studies. These exciting results need further confirmation in larger studies, and the utility of using this blood test rather than imaging to adjust treatment in advanced disease requires study as well.

Endoscopy

For gastrointestinal NETs, endoscopy with biopsy should be performed to obtain pathological diagnosis [20]. Endoscopic imaging is insufficient for definitive diagnosis as differential diagnosis includes other subepithelial lesions, such as gastrointestinal stromal tumor especially in the stomach and duodenum and cysts and Brunner's gland hyperplasia also in the duodenum. When imaging modalities fail to localize a small bowel tumor, video-capsule endoscopy (VCE) and device-assisted enteroscopy (DBE) are often needed[10]. VCE has a diagnostic yield of 45% for detecting tumors in the small intestine[65]. A retrospective study conducted over a seven year period found that small bowel tumors were detected in 1.5% of patients undergoing VCE (with a mean number of 4.7 tests used prior to VCE)[66]. In a study of 390 patients with metastatic NETs, radiology failed to localize a primary tumor in 2.8% whereas VCE identified NETs in 8/10 patients, which were confirmed histologically. As such, VCE should be used in select patients to identify small intestine NETs. While more invasive, antegrade and retrograde DBE may serve as an adjunctive tool prior to surgery by providing a histologic diagnosis and allowing tattooing areas of interest for surgeons[65]. Its diagnostic yield for detecting small intestine NETs ranges from 33%-80%[67,68]. Multifocal small intestinal NETs occur in 20%-30% of patients. CT and MRI have low accuracy for detecting these, and while CT or MR enterography, VCE, and DBE improve detection, the gold standard remains digital palpation of the small bowel intraoperatively[69].

EUS is valuable for diagnosing pancreatic NETs and differentiating from pancreatic adenocarcinoma or metastatic disease with 87.2% sensitivity of 87.2% and 98% specificity (Figure 6)[70]. Mean detection rate of pancreatic NET for EUS is 90% while about 73% for both CT and MRI[71]. EUS identified pancreatic NET in 26% of cases where CT and other radiology studies including MRI and PET were negative[72]. EUS is particularly helpful for detecting small pancreatic NETs < 10 mm, 68% of which were missed by CT[73]. EUS also provides more accurate size estimate than CT (11.2% *vs* 46.5% inaccurate, respectively). Therefore, in patients with suspected pancreatic NET and negative imaging, EUS should be performed.

A limitation of EUS sampling is inaccurate assessment of grade and Ki67 index compared with surgical specimens. This discordance is accentuated in tumors > 2 cm because Ki-67 immunoreactivity can be focal and therefore, potentially missed by EUS sampling[74]. EUS-FNB may improve assessment of Ki-67 as well as diagnostic yield compared with EUS-FNA[75,76]. Diagnostic yield of EUS-FNA in cystic pancreatic NETs is lower at 73% compared with solid NETs although higher than mucinous cysts. Cystic pancreatic NETs may have thick wall with low carcinoembryonic antigen levels (< 5 ng/mL)[77].

Adjunctive EUS technologies include elastography and contrast harmonic EUS (CH-EUS). Elastography assesses the relative stiffness of tissue qualitatively and semi-quantitatively with strain elastography and more recently shear wave elastography. It may help differentiate pancreatic ductal adenocarcinoma from pancreatic NET, but was unable to distinguish NET from benign lesions in one study[78]. Another study suggested modest ability to diagnose malignant *vs* benign pancreatic NETs (67% sensitivity and 71% specificity)[79]. Further studies are needed with shear wave elastography, which may lead to improved results. CH-EUS uses intravenous microbubble-based contrast agents to assess microvasculature in lesions. With pancreatic NETs being hypervascular, they appear hyperenhancing on CH-EUS with sensitivity 79% and specificity 99%[80]. CH-EUS may be particularly helpful in assessing tumor grade as microvasculature density inversely correlates with grade. Therefore, higher grade tumors have more heterogeneous enhancement with 90% accuracy for predicting malignancy and > 95% negative predictive value for tumor aggressiveness[81]. Quantitative CH-EUS may allow accurate differentiation of G1/G2 pancreatic NET from G3 pancreatic NEC[82].

MANAGEMENT

The next sections will highlight updates and controversial areas needing further research for the various GEP-NETs.

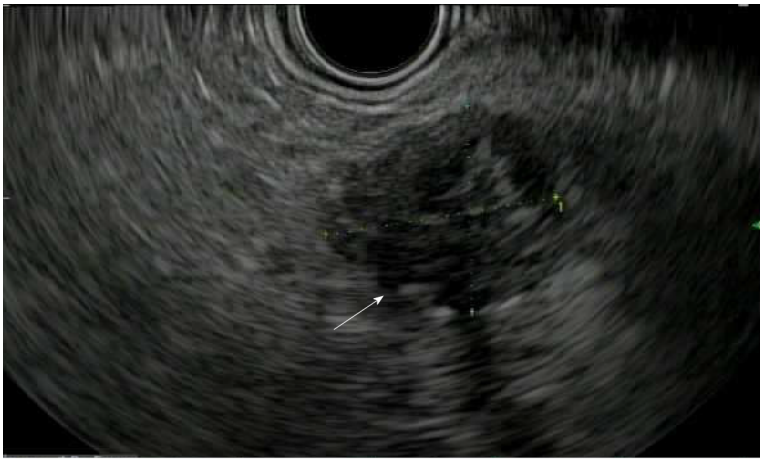

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Figure 6 Endoscopic ultrasound of pancreatic neuroendocrine tumor appearing well-defined and hypoechoic.

Stomach

Gastric NETs are typically diagnosed incidentally during endoscopy, and it is important to understand the subtypes of gastric NETs and their corresponding treatment recommendations (Table 2). Metastases occur in less than 10% of type I gastric NETs ≤ 2 cm (Figure 7), but in nearly 20% greater than 2 cm[83,84]. A long-term study of small (< 1 cm) type I gastric NETs followed endoscopically over an average of 7 years found that none developed advanced disease or significant growth of the tumor[85]. For larger lesions, EUS should be performed to assess depth of invasion and presence of lymph node metastases before performing endoscopic or surgical resection. Regarding endoscopic resection, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) can be considered although ESD should be reserved for larger lesions with superficial submucosal invasion[86]. A retrospective study of 87 Lesions less than 1 cm resected by ESD or EMR found that while complete resection rates trended higher with ESD (94.9% *vs* 83.3%, $P = 0.174$), it was associated with increased procedural time (26.1 min *vs* 9.5 min) and a tendency towards higher complications (15% *vs* 6%, $P = 0.28$)[87]. For rare type 1 gastric NETs with invasive disease, regional metastases, or grade 3 Lesions, surgery may be considered [88]. Antrectomy is an option in patients with numerous tumors, which may be curative with decreased recurrence compared to endoscopic resection (11% *vs* 44%)[89]. The role of medical therapy with SSAs (lanreotide and octreotide) to suppress gastrin levels as a means to reduce tumor progression remains to be determined[86].

Because type III gastric NETs behave differently from type I and II and are very aggressive tumors, traditionally surgical resection was recommended (Table 3)[90,91]. However, for small < 1 cm well-differentiated lesions without EUS evidence of deep invasion or regional metastases, endoscopic resection may be feasible[92]. A Japanese multi-center study of 144 Lesions (90 G1 and 54 G2) with median size 8 mm compared surgical (81 patients) and endoscopic (63 patients) resection outcomes during long-term follow-up[93]. Patients undergoing endoscopic resection had smaller lesions confined to the mucosa or submucosa, and 24% of these patients needed subsequent surgical resection. Overall, 5-year survival was similar for both groups, and in the endoscopic resection alone cohort, only one patient developed recurrence with no mortality over median 32-mo follow-up. Another recent study comparing 45 patients undergoing surgical or endoscopic resection found that tumor size greater than 1 cm was associated with lymph node metastases[94]. In a cohort of 50 patients undergoing endoscopic resection (41 EMR and 9 ESD) with a median follow up of 46 mo, mean size was 10 mm with nonsignificant trend towards larger lesions resected with ESD (14.2 mm *vs* 9.3 mm) and greater lymphovascular invasion in ESD patients (22.2% *vs* 2.4%). However, there was no evidence of tumor recurrence in either group. Of note, all lesions were no deeper than the submucosa layer and well-differentiated[95]. Given the more aggressive biology of type III gastric NETs, ESD may be favored over EMR although further study is needed. The resection approach should be carefully tailored to a patient's tumor size, depth of invasion, grade and presence of regional metastases[71].

Duodenum

Table 3 summarizes evaluation and management of small intestinal (duodenal, ampullary, and jejuno-ileal) NETs[96,97]. Nearly 90% of duodenal NETs are non-functional, well-differentiated and incidentally discovered as small, polypoid lesions in the first and second portion of the duodenum (Figure 8)[88]. For small duodenal NETs undergoing EMR, the optimal EMR technique remains unclear (standard, underwater, ligation, ligation without resection) with the main complications being bleeding in up to 20% of patients and perforation. For lesions greater than 2 cm without evidence of metastatic

Table 2 Gastric neuroendocrine tumors[88,90,91]

	Type 1	Type 2	Type 3	Type 4
Proportion of gastric neuroendocrine tumors	70%-80%	5%	15%-25%	Very rare
Associated conditions	Atrophic gastritis	Zollinger-Ellison and MEN-1	Sporadic	Sporadic
Location	Gastric fundus and body	Gastric fundus and body	Antrum	Anywhere
Endoscopic findings	Multiple, small polyps	Multiple, small polyps	Solitary, larger	Solitary, larger
Gastrin level	Increased	Increased	Normal	Normal
pH	Increased	Decreased	Normal	Normal
Prognosis	Excellent	Good	Poor	Very poor
Metastasis	10%-20%	10%-30%	30%-80%	80%-100%
Evaluation	Gastric pH, gastrin, EUS 1-2 cm lesions	Gastric pH, gastrin, EUS 1-2 cm lesions, abdominal imaging	Gastric pH, gastrin, EUS, abdominal imaging	Gastric pH, gastrin, EUS, abdominal imaging
Treatment	Endoscopic resection for larger lesions and surveillance for lesions < 2 cm	Similar to type 1	Surgery, endoscopic resection for superficial, well-differentiated lesions < 1 cm	Surgery for local disease, systemic chemotherapy for metastatic
Surveillance	EGD every year	EGD every 6-12 mo, abdominal imaging every year	EGD every 6-12 mo, abdominal imaging every 3 mo	

EUS: Endoscopic ultrasound; EGD: Esophagogastroduodenoscopy; MEN1: Multiple endocrine neoplasia type 1.

Table 3 Small intestinal neuroendocrine tumors[96,97,101,102,104,108,109]

	Duodenal	Ampullary	Jejuno-ileal
Epidemiology	2%-3% GEP-NETs	0.3%-1% GEP-NETs	1.2 cases/100000 incidence quadrupled over past 30 yr
Evaluation	> 2 cm: CT and EUS	CT, EUS	Chromogranin A, urine 5-HIAA, CT/MRI, gallium-DOTATATE PET CT, colonoscopy into terminal ileum
5-yr survival	No metastases: 80%-95%; Regional metastases: 65%-75%; Zollinger-Ellison or MEN-1: > 90%	59%	Local disease: 80%-100%; Regional disease: 70%-80%; Distant metastases: 35%-80%
Treatment	< 1 cm: Endoscopic resection; 1-2 cm: Endoscopic or surgical resection; > 2 cm: EMR or ESD, surgical resection for regional disease	< 2 cm superficial without metastases: Pancreaticoduodenectomy or consider endoscopic ampullectomy; > 2 cm: Pancreaticoduodenectomy	Surgery; Carcinoid syndrome: Long-acting SSA (octreotide LAR 20-30 mg IM)
Surveillance	EGD at least every 2 yr	EGD at 1-2 yr interval	NANETS: Curative surgery-CT every 3-6 mo then 6-12 mo for 7 yr; Advanced disease- CT every 6 mo; ENETS: Curative surgery: Chromogranin A, urine 5-HIAA, CT every 6-12 mo; Slow-growing treated without curative intent: every 3-6 mo

EUS: Endoscopic ultrasound; EGD: Esophagogastroduodenoscopy; GEP-NETs: Gastroenteropancreatic neuroendocrine tumors; PET: Positron emission tomography; CT: Computed tomography; MRI: Magnetic resonance imaging; SSAs: Somatostatin analogues; LAR: Long-acting release; HIAA: Hydroxyindoleacetic acid.

disease, ESD should be reserved for larger lesions because perforation and bleeding appear higher than with EMR or ESD[20,86,98].

The optimal strategy for duodenal NETS between 1 and 2 cm remains unclear. A multicenter study of 60 patients found that lesions larger than 11 mm had significantly higher rates of lymphovascular invasion and incomplete endoscopic resection with none having complete pathologic resection compared with smaller lesions[99]. Therefore, the authors suggested surgical resection for lesions larger than 11 mm. However, a recent study suggested EMR is efficacious and safe for 1-2 cm lesions without regional or distant metastases with similar overall survival to surgical resection during median 56-mo follow-up[100]. As expected, patients undergoing EMR were older (72.6 years *vs* 59.2 years,

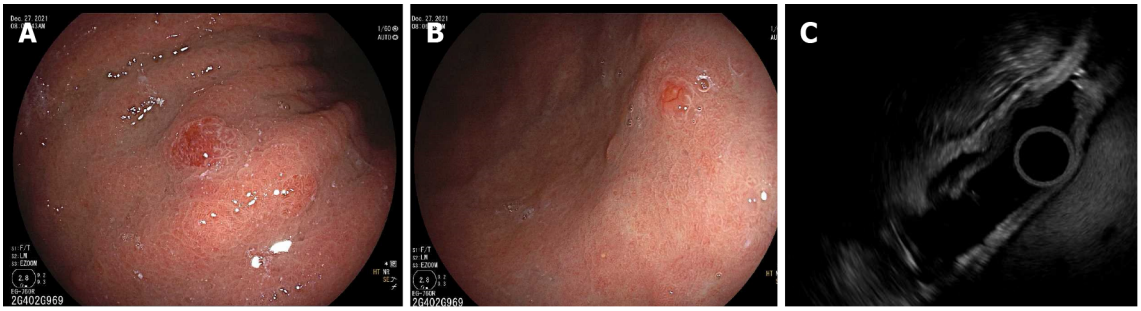

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Figure 7 Endoscopic and endoscopic ultrasound views of type 1 small, superficial neuroendocrine lesions in gastric body. A and B: Endoscopic; C: Endoscopic ultrasound.

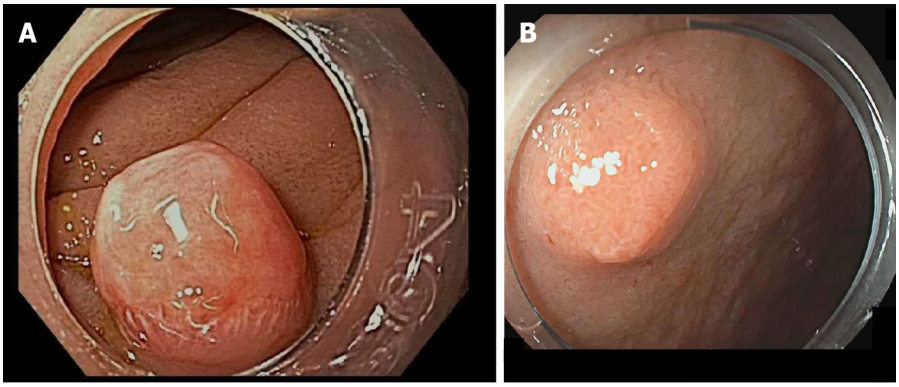

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Figure 8 Endoscopic imaging of duodenal neuroendocrine tumors.

respectively) with more node negative disease (89.5% *vs* 50%, respectively). The decision to pursue endoscopic or surgical resection should be considered based on local expertise and the individual case.

Ampullary NETs (Table 3) appear different in nature than non-ampullary duodenal NETs, and are often more advanced at presentation (G3 in 17% *vs* 2% for duodenal NETs) with higher incidence of lymph node metastasis (34% *vs* 10% for duodenal NETs)[101,102]. In a large pathology series of 203 duodenal NETs, most of the 27 NECs occurred in the ampullary region[103]. While pancreaticoduodenectomy is recommended regardless of size, its morbidity and mortality make endoscopic resection an attractive option. Small ampullary NETs less than 2 cm without muscularis propria invasion or lymph node metastases were completely resected endoscopically in one small study, and 71% had no recurrence during median 56 mo follow-up[104]. Further studies are needed to understand which patients may be managed with endoscopic ampullectomy.

Jejuno-ileal tumors

The true incidence of jejuno-ileal NETs (Table 3) likely remains underappreciated as in autopsy studies, the incidence is much higher (1.2 cases per 100000) than in population studies (0.67 cases per 100000)[96,105]. This implies that many early jejuno-ileal NETs remain undiagnosed[106]. Early diagnosis remains challenging as most patients are asymptomatic or have nonspecific symptoms, and carcinoid syndrome occurs in only 20%-30% of patients with metastatic disease[106]. Unlike gastric, duodenal and colorectal NETs, incidental diagnosis of jejuno-ileal NETs is unlikely with 89% found in the ileum[105,107].

Segmental resection and wide lymphadenectomy is the definitive approach for jejuno-ileal NETs with localized and regional metastatic disease[108]. Intraoperative exploration with small bowel palpation is recommended as up to 70% of pre-operative imaging may understage tumors[109]. This is likely due to limitations of diagnostic imaging including VCE and DBE, which may miss small, multifocal lesions[52,110]. For patients with distant metastatic disease, surgical resection of the primary tumor may still be considered to alleviate symptoms resulting from the lesion (for example, obstructive symptoms or bleeding), to achieve potential cure if the distant metastases may be completely resected as well, and to improve outcome although data on this is mixed and further study is needed[106].

Appendiceal tumors

Traditionally appendiceal NETs were the most common appendiceal tumors although recent data

suggests mucinous neoplasms may have surpassed them[111,112]. Most present incidentally and are asymptomatic as the majority are located in the distal one-third of the appendix rather than the base. Because risk of metastases correlates with tumor size, recommendations for evaluation and management vary depending on the size (Tables 4 and 5). However, a study of 418 patients noted that risk of nodal metastases was affected by age, depth of invasion, extent of surgery as well as tumor size with 0.89 area under the curve[113]. Another study analyzing 435 patients found that tumor size > 1.5 cm, G2 grade, lymphovascular infiltration, and mesoappendiceal invasion were associated with nodal metastasis[114]. Therefore, some guidelines suggest right hemicolectomy for 1-2 cm tumors with any of these high-risk features. However, in a study of 916 patients with 1-2 cm NETs, right hemicolectomy was not associated with increased survival despite being associated with larger and higher stage tumors (hazard ratio = 1.14, P = 0.72)[115]. The most appropriate surgical approach for appendiceal NETs especially between 1-2 cm remains unclear as well as the definitive triggers to send a patient for completion right hemicolectomy.

Colonic neuroendocrine tumors

With increased colon cancer screening, the incidence of colonic NETs has increased dramatically from 0.02 to 0.2 per 100000 people in the United States between 1973 to 2004[116]. The majority are high-grade, poorly differentiated lesions that typically occur in the right colon (70%), especially in the cecum [117,118]. Well-differentiated colonic NETs have significantly worse prognosis than well-differentiated NETs anywhere else in the GI tract. A recent study using the SEER database developed a novel nomogram to predict survival incorporating patient's age ≥ 68 years, sex, tumor size, grade, chemotherapy, N stage and M stage. This outperformed the traditional TNM staging system in predicting overall survival[119].

With aggressive behavior and poor survival outcomes, colonic NETs require multidisciplinary care (Table 5). Tumors < 2 cm may be considered for endoscopic resection, however surgery is required for incomplete resection or high-grade pathology[116]. Very little data exists about the efficacy and safety of ESD with one study including only 6 non-rectal, colonic NETs. This study demonstrated that non-rectal NETs were significantly associated with risk of non-R0 resection and while complications were higher, this was not significant compared with ESD of rectal NETs[120]. On the other end of the spectrum in patients with metastatic disease, chemotherapy can also be utilized[117]. Survival improved with chemotherapy alone, surgery alone and even more with the combination of surgery and chemotherapy (5-year survival 37% for combination *vs* 32% surgery alone, P < 0.001)[121]. However, other studies noted that surgery did not provide significant survival benefit in localized and metastatic disease[122, 123]. Further study is necessary to understand the optimal treatment combination as well as role of immunotherapy.

Rectal neuroendocrine tumors

Similar to colonic NETs, rectal NETs have been increasingly diagnosed with improved screening colonoscopy rates, experiencing a 10-fold rise in incidence over the past 30 years[124,125]. They are more common in women in the United States although in Korea men are more likely to have rectal NETs. In the United States, Asian and African American patients have higher incidence than Caucasians [126]. The majority (70%-88%) of rectal NETs are small (< 1 cm) and localized at the time of diagnosis [124,127]. Lymph node metastasis occurs in about 2% and distant metastases in about 8% of rectal NETs at diagnosis. Tumor size, depth of invasion, grade and lymphovascular invasion all affect prognosis. Regarding tumor size, it appears to correlate with metastasis at the time of diagnosis (3%, 66%, and 73% metastases with tumor size ≤ 1 cm, 1-1.9 cm, and ≥ 2 cm, respectively)[128]. A study using the SEER database of 788 patients with T1 rectal NETs noted tumor size and submucosal invasion were predictive of metastasis, and no tumors ≤ 19 mm without submucosal invasion had metastases[129]. At diagnosis, 1.5% of patients had metastases with 1.1% in tumors ≤ 10 mm and 6.6% in NETs 11-19 mm.

Usually, rectal NETs are not recognized before polypectomy by the endoscopist and only later discovered when pathology returns. If the endoscopist is suspicious of a rectal NET during the procedure, biopsies can be obtained with photograph documentation and tattoo adjacent to the lesion. In terms of treatment, endoscopic resection should be performed for lesions smaller than 1 cm without invasion beyond the submucosa. Options include EMR, EMR band ligation, and ESD; however, given the greater procedure time and complications with ESD, EMR or EMR band ligation are preferred. A prospective study comparing EMR band ligation (n = 53) to ESD (n = 24) in lesions ≤ 10 mm demonstrated the superiority of EMR band ligation with higher complete resection rates (100% *vs* 54.2%, P = 0.00)[130]. In addition to 100% negative margins, EMR band ligation was associated with shorter procedure times (5.3 *vs* 17.9 min, P = 0.00). Similarly, a retrospective study of 82 tumors < 10 mm reported higher complete resection rates with EMR band ligation compared to ESD (95% and 75%, P = 0.025) with shorter procedure times[131]. A recent retrospective comparative study of underwater EMR (n = 36) to ESD (n = 79) found no difference in achieving R0 resection for lesions ≤ 10 mm[132]. Yet underwater EMR was associated with a significantly shorter procedure time (5.8 min *vs* 26.6 min, P = 0.0001) and no adverse events while there were two cases of delayed bleeding and minor perforation in the ESD group. Therefore, for small rectal NETs < 1 cm, EMR band ligation is the endoscopic method of choice while underwater EMR may be considered as well.

Table 4 Risk of metastases by tumor size in appendiceal neuroendocrine tumors[169]

Tumor size	Nodal metastases	Distant metastases
≤ 1 cm	0%	0%
1-2 cm	7.5%	4%
≥ 2 cm	33%	12%

Table 5 Colorectal neuroendocrine tumors[103,112,114,121,124,126,170-173]

	Appendiceal	Colonic	Rectal
Epidemiology	1.45% of appendectomies	< 10% NETs	29% GEP-NETs
Presentation	Incidental or acute appendicitis; Carcinoid syndrome rare	Incidental (yellowish polypoid or donut-shaped); 46% advanced at diagnosis	Incidental (small, yellowish polypoid)
Evaluation	(1) Colonoscopy; (2) CT/MRI if > 2 cm, incomplete resection[1], suspected metastases; (3) Gallium DOTATATE PET CT: Incomplete resection[1], suspected metastases, carcinoid syndrome; and (4) Chromogranin A and urine 5-HIAA: liver metastases or carcinoid syndrome	CT, EUS, Gallium DOTATATE PET CT	Colonoscopy; EUS; > 2 cm, invasion beyond submucosa, lymph node disease: Gallium DOTATATE PET CT
5-yr survival	< 2 cm without regional or distant disease: 100%; 2-3 cm with regional nodes or ≥ 3 cm: 78%; Distant metastases: 32%	Stage I: 90%; Stage II: 77%; Stage III: 53%; Stage IV: 14%	Localized: 98%-100%; Regional metastases: 54%-74%; Distant metastases: 15%-37%
Treatment	Right hemicolectomy with lymph node dissection: (1) > 2 cm; and (2) 1-2 cm with high-risk features[2]; Appendectomy: (1) < 1 cm, well-differentiated; and (2) 1-2 cm without high-risk features[2]	Local disease: segmental colectomy and lymphadenectomy; Metastatic disease: chemotherapy	< 1 cm without invasion beyond submucosa: Endoscopic resection; 1-2 cm: Endoscopic resection or transanal resection; > 2 cm without metastatic disease: Radical surgical resection
Surveillance	(1) ≤ 2 cm without high-risk features[2] and confined to appendix: No follow-up; and (2) Larger or node positive, and right hemicolectomy: CT/MRI 3-12 mo post-surgery; consider baseline gallium DOTATATE PET CTAfter first year, annual CT/MRI		< 1 cm: None; 1-2 cm: EUS or MRI at 6 and 12 mo; > 2 cm: CT/MRI at 3 and 12 mo, then every 12-24 mo

[1]Incomplete resection: Positive margin and/or lymph nodes.

[2]High-risk features: Large tumor size, G2, lymphovascular invasion, mesoappendiceal invasion.

NET: Neuroendocrine tumor; EUS: Endoscopic ultrasound; EGD: Esophagogastroduodenoscopy; GEP-NENs: Gastroenteropancreatic neuroendocrine neoplasms; PET: Positron emission tomography; CT: Computed tomography; MRI: Magnetic resonance imaging; HIAA: Hydroxyindoleacetic acid.

If incomplete resection occurs, then salvage therapy with ESD or transanal endoscopic microsurgery should be pursued to minimize recurrence[133,134]. Optimal management for rectal NETs 1-2 cm remains uncertain. NANETS recommends transanal excision although noted this could be considered after endoscopic resection if that resulted in positive margins. ESD may have a role and may be preferred to cap-assisted EMR as higher complete resection (100% *vs* 70%) and lower recurrence (0% *vs* 17%) was achieved with ESD[135]. However, ESD may not be the ideal approach in patients with lymphovascular invasion, grade 2, and/or positive margins as distant metastasis occurred in 2.5% following ESD of small (< 2 cm) rectal NETs[120]. With advanced metastatic disease, palliative surgery and systemic therapies should considered through a multidisciplinary approach considering availability of local resources.

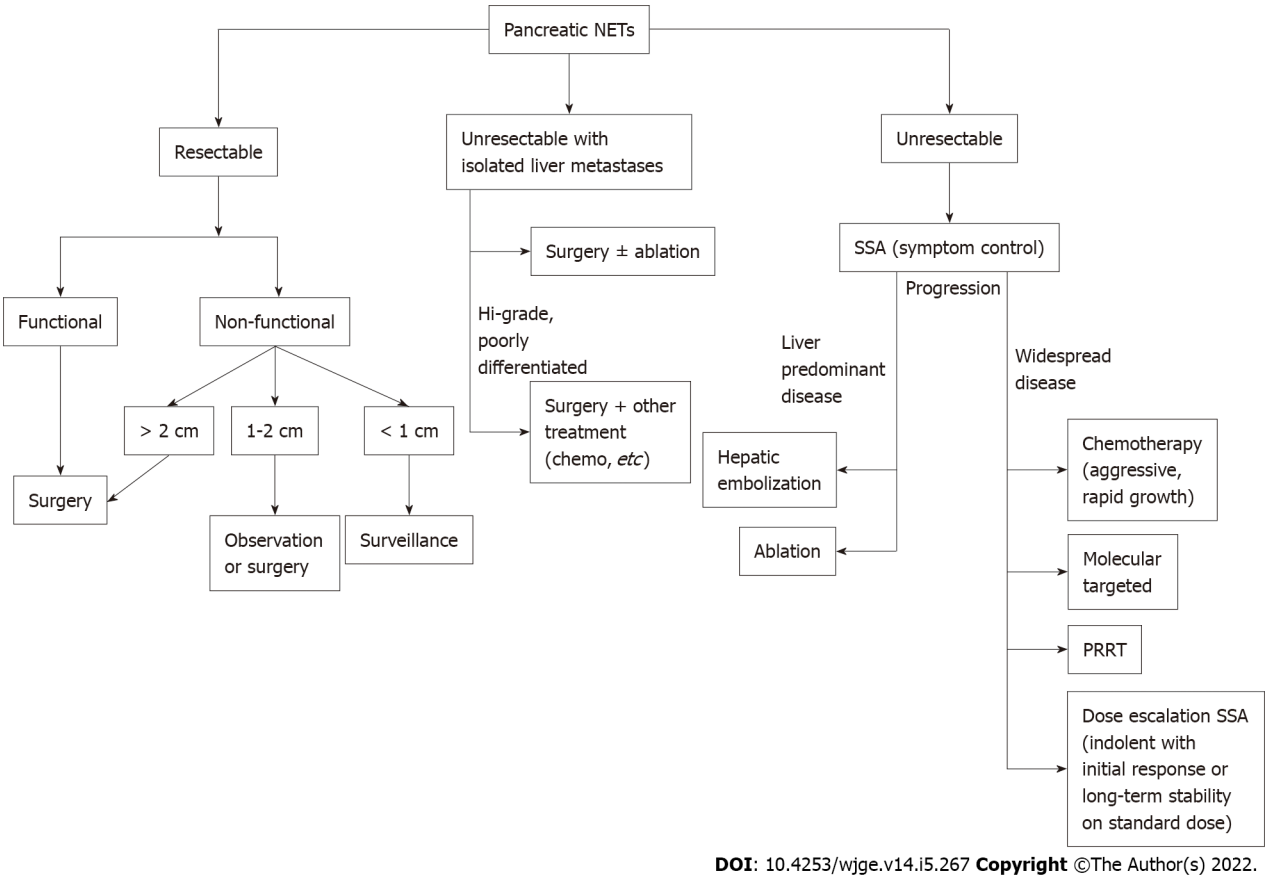
Pancreas

Pancreatic NETs make up 16% of GEP-NETs with annual incidence of 0.5 per 100000 people[6,9]. The majority are sporadic and malignant with metastatic disease present in 60% of patients at the time of diagnosis (Table 6)[96,136]. If there are no distant metastases or if the metastatic disease is resectable (for example, isolated hepatic metastases), surgery is the primary method of treatment for all functioning pancreatic NETS, irrespective of size (Figure 9). It is also recommended for localized (confined to the pancreas and regional lymph nodes) nonfunctioning pancreatic NETs greater than 2 cm. Lesions less than 1 cm can safely undergo surveillance in the absence of symptoms and pancreatic duct dilation [137]. In a cohort comparing nonoperative and operative management of nonfunctioning NETs less than 1 cm, there was no difference in mortality or disease progression over median 45-mo follow up with surgical patients experiencing relatively high 46% rate of complications postoperatively[138].

Table 6 Diagnosing pancreatic neuroendocrine tumors[136,174]

	Diagnostic evaluation
All pancreatic NET	Multiphasic CT/MRI
	If results impact management, gallium DOTATATE PET CTEUS with biopsy
Insulinoma	72 h fast test: Hypoglycemia with elevated insulin
	Oral glucose tolerance test: May be necessary in minority with only postprandial hypoglycemia
Gastrinoma	Fasting gastrin 10 times upper limit of normal + gastric pH < 2
	If gastrin less elevated + gastric pH < 2, measure BAO with secretin test
	BAO > 15 mEq/h or serum gastrin increase > 120 pg/mL
Glucagonoma	Fasting serum glucagon > 500 pg/mL
Somatostatinoma	Fasting plasma somatostatin > 30 pg/mL
VIPoma	Large volume diarrhea + serum VIP > 75 pg/mL

NET: Neuroendocrine tumor; CT: Computed tomography; MRI: Magnetic resonance imaging; PET: Positron emission tomography; EUS: Endoscopic ultrasound; BAO: Basal acid output.



DOI: 10.4253/wjge.v14.i5.267

Figure 9 Treatment algorithm for pancreatic neuroendocrine tumors. NET: Neuroendocrine tumor; SSA: Somatostatin analogue; PRRT: Peptide receptor radionuclide therapy.

However, observation *vs* surgery for nonfunctioning pancreatic NETs measuring between 1-2 cm remains controversial. Several studies have supported observation, as smaller tumor size correlates with lower malignancy potential[138-141]. On the other hand, other studies have suggested surgery is superior[142-145]. One study that followed 39 resected lesions less than 2 cm for a median 34.2 mo found that 7.7% developed late metastasis or recurrence[143]. Two other comparative studies supported surgical resection for pancreatic NETs less than 2 cm, as five-year overall survival rates were greater than the observation group (82.2%-92.8% *vs* 34.3%-67.4%, respectively)[142,145]. Regardless of tumor

size, if surgery is pursued, follow up with cross-sectional imaging is recommended annually for the first three years then every two years for a total of 10 years[146].

EUS-guided radiofrequency ablation (RFA) has recently been studied as a potentially safe and minimally invasive treatment option. Through the use of targeted electromagnetic energy and alternating high-frequency currents, EUS-RFA induces coagulative necrosis, fibrotic changes, and a delayed immune response to the pancreatic tissue of interest[147]. Only a few human studies have investigated treatment outcomes, but have demonstrated feasible and promising results[148,149]. In one study, 18 patients (including seven insulinomas and 11 non-functioning lesions) with a mean diameter of 1.4 cm demonstrated no signs of recurrence during mean follow-up of 8.7 mo[149]. Furthermore, all seven patients with insulinomas had normalization of glucose within 24 h of EUS-RFA. A prospective multicenter study of 14 pancreatic NETs (G1 lesions with median size 1.3 cm) found that 12 (85.7%) lesions completely resolved at 12 mo follow up[148]. The other two lesions were considered treatment failures with one increasing by 3 mm and the other remaining unchanged in size. A recent video case report used EUS-guided microwave ablation to safely and effectively treat a symptomatic inoperable pancreatic neck NET (35 × 32 mm) invading the splenic artery without any complications[150]. Further prospective and longer-term studies are needed to determine how this technology may improve patient outcomes and how it fits into the treatment algorithm.

For patients with isolated liver metastases, optimal management remains uncertain in the absence of randomized controlled studies and ranges from surgical resection of all visible metastatic disease to local therapy with ablation. Candidates for resection of liver metastases include those with isolated unilobar disease, preserved liver function and well-differentiated pathology[151]. However, even patients with bilobar disease could undergo multiple wedge resections and/or hepatectomy provided at least 20 percent of the total liver volume remains preserved. Five-year survival rates ranging from 85% to 90% have been reported with selected patients undergoing curative resection[152,153]. However, recurrence rates are as high as 54% despite negative margins, which implies that preoperative imaging misses small metastatic disease[154].

Whether the primary tumor should be resected as well in these patients remains debated although retrospective studies suggest improved survival with this approach[155].

Ablation is mainly effective for small (< 3 cm) lesions and includes RFA, cryoablation and microwave ablation with a more favorable morbidity profile than surgery or hepatic arterial embolization. The optimal use of this technique remains unclear although it is often used as an adjunct to surgical resection especially when complete resection of multifocal or bilateral disease is not feasible or in patients who have already undergone hepatic resection. Comparative studies remain limited with one nonrandomized study suggesting high overall 5-year survival (84%) following RFA compared to surgery (90%)[152]. If RFA is contraindicated (especially for lesions near the liver surface or adjacent to vital structure) or technically not possible, cryoablation can be used[156]. While cryoablation is relatively underutilized, a small case series demonstrated 77.8% complete response and 22.2% partial response in 9 patients undergoing ablation with a median follow of 7 mo[157]. Cryoablation may be considered in technically challenging tumor locations. Further studies are needed to delineate its role relative to other ablative techniques.

For unresectable liver disease in symptomatic patients, hepatic arterial embolization is suggested for palliation as an alternative to medical treatment alone. Techniques include injection of different substances [bland embolization (gel foam powder), chemoembolization (chemotherapy), radioembolization (radioactive isotopes)]. In liver predominate disease, chemoembolization is associated with a tumor response rate over 50%, which appears comparable to the other techniques[158]. A randomized trial is underway to compare liver progression-free survival and complications of these three techniques.

For unresectable widespread disease, treatment options include systematic therapy with SSAs to treat symptoms and control disease, chemotherapy, molecular targeted therapy, PRRT, and immunotherapy. SSAs suppress hormone release in pancreatic NETs by binding somatostatin receptors, which prevents the release of hormonal peptides, and is thus most helpful for VIPomas, glucagonomas, and somatostatinomas and less helpful for insulinomas and gastrinomas. When used to control disease by exploiting the ability of SSAs to decrease proliferation in nonfunctioning NETs, SSAs are administered to patients with high tumor burden[159]. The CLARINET study, a randomized, double blind placebo trial, provided support for lanreotide in preventing disease progression in advanced well to moderately differentiated nonfunctioning pancreatic NETs (prolonged progression-free survival 65% *vs* 33% at 24 mo)[160]. Short-acting octreotide may be used and if effective, changed to long-acting depot with monthly injections.

Chemotherapy is particularly helpful in aggressive disease with rapidly growing metastases[10]. Compared to temozolomide, the use of combination chemotherapy with capecitabine and temozolomide (CAPTEM) demonstrated high response, progression free survival, and manageable toxicity in patients with well-differentiated intermediate to high grade pancreatic NETs[161,162]. Given its favorable toxicity profile as an oral regimen, CAPTEM is typically favored over streptozocin-containing regimens. Expression of methylguanine DNA methyltransferase (MGMT) may predict response to alkylating chemotherapeutics as studies suggested that patients without MGMT had better response [163]. However, prospective studies are necessary.

Molecular targeted therapy has a role in patients with disease progression on SSAs by inhibiting the mammalian target of rapamycin or tyrosine kinase with everolimus and sunitinib, respectively[164]. Compared to placebo, everolimus was able to prolong progression free survival (11 mo *vs* 4.6 mo) in a cohort of 410 patients with advanced, progressive low and intermediate grade pancreatic NETs[165]. Sunitinib has also demonstrated safe and reliable results in progressive, well-differentiated pancreatic NETs where progression free survival was double placebo (11.4 mo *vs* 5.5 mo)[161]. with a response rate of 24.5%[166]. Other promising agents include tyrosine kinase inhibitors sorafenib, pazopanib, vascular endothelial growth factor receptor inhibitor cabozantinib and lenvatinib, which all require further prospective study.

PRRT uses radiolabeled SSAs (^{90}Yttrium or ^{177}Lutetium) to bind somatostatin receptors as a means to emit localized radiation in advanced pancreatic NETs[164]. Therefore, it is an option in patients who have progressed through SSAs. A phase III trial compared ^{177}Lu-Dotatate (116 patients) to long acting octreotide (113 patients) and found longer progression free survival (65.2% *vs* 10.8%) and higher response rates (18% *vs* 3%) with ^{177}Lu-Dotatate[167]. A larger study of 610 patients (which included bronchial NETs) also reported a favorable survival and response rate, especially in the pancreatic NET group[168]. Despite encouraging results, concern remains over potential long-term toxicity including acute leukemia (0.7%) and myelodysplastic syndrome (1.5%)[168]. As such, risk and benefits of treatment should be carefully discussed with patients before embarking on PRRT. Further studies are needed to understand the role and safety of PRRT as well as whether combination therapy with SSAs is more efficacious.

Although immunotherapy has revolutionized oncology, its utility in treating pancreatic NETs remains unclear. Early trials evaluating anti-programmed cell death 1 antibodies including spartalizumab and pembrolizumab have not been encouraging with minimal response in pancreatic NETs. Further studies are certainly needed.

CONCLUSION

GEP-NENs represent a complex and diverse physiologic and pathologic spectrum of neoplasms with varying disease activity that benefit from multidisciplinary care. With advancements in functional imaging, serum biomarkers, and endoscopic techniques for diagnosis including EUS as well as therapy with EMR, ESD and EUS-RFA, identification and management of these protean lesions continue to improve and allow for tailored treatment plans based on prognostic information and location throughout the gastrointestinal tract.

FOOTNOTES

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Abstract

The differential diagnosis between benign and malignant biliary strictures is challenging and requires a multidisciplinary approach with the use of serum biomarkers, imaging techniques, and several modalities of endoscopic or percutaneous tissue sampling. The diagnosis of biliary strictures consists of laboratory markers, and invasive and non-invasive imaging examinations such as computed tomography (CT), contrast-enhanced magnetic resonance cholangiopancreatography, and endoscopic ultrasonography (EUS). Nevertheless, invasive imaging modalities combined with tissue sampling are usually required to confirm the diagnosis of suspected malignant biliary strictures, while pathological diagnosis is mandatory to decide the optimal therapeutic strategy. Although EUS-guided fine-needle aspiration biopsy is currently the standard procedure for tissue sampling of solid pancreatic mass lesions, its diagnostic value in intraductal infiltrating type of cholangiocarcinoma remains limited. Moreover, the "endobiliary approach" using novel slim biopsy forceps, transpapillary and percutaneous cholangioscopy, and intraductal ultrasound-guided biopsy, is gaining ground on traditional endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography endobiliary forceps biopsy. This

review focuses on the available endobiliary techniques currently used to perform biliary strictures biopsy, comparing the diagnostic performance of endoscopic and percutaneous approaches.

Key Words: Biliary strictures; Endoscopic retrograde cholangiography; Cholangioscopy; Endobiliary forceps biopsy; Intraductal ultrasound-guided biopsy; Percutaneous transhepatic

Core Tip: Invasive imaging modalities combined with tissue sampling are almost always required to confirm the diagnosis of suspected malignant biliary strictures. The "endobiliary approach" using novel slim biopsy forceps, transpapillary and percutaneous cholangioscopy, and intraductal ultrasound-guided biopsy is gaining ground over traditional endoscopic retrograde cholangiopancreatography and percutaneous endobiliary forceps biopsy. Nevertheless, both endoscopic and percutaneous interventional radiology modalities are today considered safe and effective tissue sampling options, providing histologic identification of biliary strictures with satisfactory sensitivity and specificity rates.

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INTRODUCTION

The diagnosis of biliary strictures remains a challenge, even in an era of considerable technologic advances regarding our current diagnostic tools. A biliary stricture is an area of stenosis in the intrahepatic or extrahepatic biliary tree (Figure 1). It can be the result of either malignant or benign pathologies, with a high prevalence of malignancy (two-third of cases)[1]. Malignant strictures of the biliary system (MBS) are commonly divided into distal strictures (involving the common bile duct) and proximal strictures (involving the hepatic hilum and right and left hepatic ducts). Pancreatic ductal adenocarcinoma is the most common cause of distal malignant stenosis, followed by cholangiocarcinoma, and, less commonly, ampullary or metastatic cancer. Proximal malignant strictures are due to cholangiocarcinoma, hepatocellular and gallbladder cancer or lymphoproliferative disorders, and metastatic lesions. The most common causes of a benign stricture include iatrogenic injury, chronic pancreatitis, primary sclerosing cholangitis, autoimmune diseases, and others. Biliary strictures are defined indeterminate when a clear diagnosis cannot be obtained after a non-invasive diagnostic work-up and an endoscopic retrograde cholangiopancreatography (ERCP) with biliary sampling. Their evaluation should be extremely careful given the noteworthy false-positive preoperative diagnosis of cancer, resulting in a 13%-24% resection rate of benign lesions[2].

Differentiating between the nature of strictures and diagnosing the relative aetiology often require a complex diagnostic approach. The evaluation of biliary strictures consists of laboratory markers and invasive and non-invasive imaging examinations including focused abdominal ultrasound (US), computed tomography (CT), contrast-enhanced magnetic resonance cholangiopancreatography, and endoscopic ultrasonography (EUS).

Nevertheless, invasive imaging modalities combined with tissue sampling are almost always required to support the diagnosis of a suspected MBS. If a histological diagnosis is obtained through the first procedure, further invasive diagnostic modalities can be avoided and appropriate treatment can be started. Both endoscopic retrograde cholangiography (ERC) and percutaneous transhepatic cholangiography endobiliary forceps biopsy (PTHC-EFB) have been valid procedures for a while for histological assessment of intrahepatic and/or extrahepatic biliary strictures.

EUS-guided fine-needle aspiration biopsy (FNAB) is nowadays the standard procedure for tissue sampling of solid pancreatic lesions because of its high diagnostic rate: In this setting, previous meta-analyses reported that the sensitivity rates of EUS-FNAB ranged from 85% to 89%[3]. However, EUS-FNAB has some limitations in cases of MBS other than pancreatic lesions, such as the frequent intraductal infiltrating type of cholangiocarcinoma. Furthermore, over the past 20 years, the technique of EUS-guided biliopancreatic lesion sampling has not gained widespread availability.

Currently, other endobiliary techniques for biliary tissue acquisition are increasing the possibility to obtain a definitive diagnosis: In fact, the "endobiliary approach" to suspect MBS is expanding past the more traditional ERCP and PTHC, through the use of novel slim biopsy forceps, to include transpapillary and percutaneous cholangioscopy, and intraductal ultrasound-guided biopsy (IDUS-G biopsy).

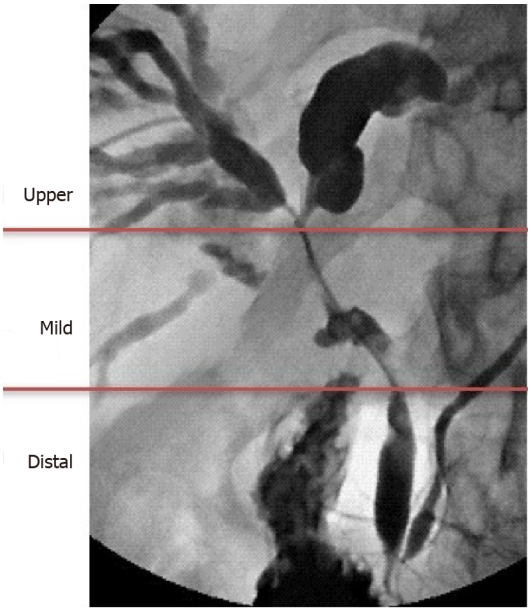

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Figure 1 Biliary stricture levels.

ENDOSCOPIC TECHNIQUES

Endoscopic retrograde cholangiopancreatography

ERCP is a diagnostic and therapeutic invasive imaging modality that provides an "indirect" radiological visualization of the biliopancreatic ductal system. ERCP with endobiliary brushing and/or forceps biopsy is often the first endoscopic approach for tissue sampling of biliary strictures because of its wide availability. According to several studies, the forceps biopsy sampling method has slightly better performance in comparison to brush cytology: A systematic review and a meta-analysis (9 studies; n = 730 patients) by Navaneethan *et al*[4] reported a pooled diagnostic odds ratio in detecting malignant biliary strictures of 43.18 (95% confidence interval [CI]), with a 48.1% pooled sensitivity and 99.2% pooled specificity, for intraductal biopsies, compared to a pooled diagnostic odds ratio of 33.43 (95%CI), with a 45% pooled sensitivity and 99% pooled specificity, for brushing. Combining the two sampling methods only modestly increased the sensitivity to 59.4%.

Theoretically, sufficient biliary tissue sampling provides adequate identification of the tissue's specific features such as superficial intraductal spread and/or wall invasion, details that cannot be obtained by brush cytology. Despite a low-diagnostic sensitivity, brush cytology is still the first line ERCP sampling modality, because of its feasibility and safety. However, as trans-papillary forceps biopsy has got a higher sensitivity rate in comparison to brush cytology, it may play an important role in the pathological confirmation of MBS.

Several series reported malignancy detection rates with ERCP endobiliary forceps biopsy ranging from 33% to 71 % for pancreatic cancer and 44% to 89 % for cholangiocarcinoma[5]. A more recent review by Korc and Sherman[6] reported detection rates for pancreatic cancers and cholangiocarcinoma of 37% and 63%, respectively. The poor sensitivity of endobiliary forceps biopsy is likely due to the blind modality of sampling under fluoroscopic guidance. In addition, MBS that mainly infiltrate the wall of the duct or incite extrinsic compression are challenging to be targeted through the ERCP tissue sampling modality. ERCP with trans-papillary biopsies are performed using forceps designed for standard endoscopes[6] that should provide an adequate sample of bile duct tissue deep to the epithelium. The biopsy forceps are introduced into the bile duct after sphincterotomy of the papilla, even though some studies described the forceps insertion modality without previous sphincterotomy [7]. The forceps are pushed under fluoroscopic guidance to the level of the stricture to grasp specimens from the lower part of the stricture. The ideal number of specimens to perform has not been standardized, although several studies[5-8] suggest that at least three specimens should be obtained.

To optimize the unsatisfying sensitivity of trans-papillary forceps biopsy, in 2011 Wright *et al*[9] proposed a method of rapid on-site cytopathological evaluation (ROSE) through the cytologic preparation and analysis of forceps biopsy sampling made by an onsite cytopathologist (Smash protocol). In total, 133 patients were enrolled in the study. A "smash" specimen sensibility of 72% was reported.

Another work[10] valued the yield of ERCP biliary biopsy sampling subjected to ROSE and reported that sensitivity for cancer diagnosis increased to 76%-97%. This gain suggests that ROSE modality may improve the sensitivity of ERCP forceps biopsy sampling. However, this resource is available only to a

few tertiary referral centres. Adverse events related to endobiliary forceps biopsy sampling are rare: To date, the same minor and only a few major cases of haemobilia[8] and perforation of the common hepatic duct[11] have been described.

Novel slim biopsy forceps

To overcome the difficulty of common bile duct cannulation that is related to the thickness and the hardness of the standard biopsy forceps, some novel biopsy forceps have been developed. In 2017, Inoue *et al*[11] published a study about the diagnostic yield of controllable biopsy-forceps (C-BF) in MBS. C-BF (MTW Endoskopie, Wesel, Germany) allows the tip's angle to be adjusted by up to 90°. In that study, 110 patients with biliary strictures were retrospectively evaluated. A high technical success rate (99%) of biliary biopsies sampled was reported.

That study reported different performances of the biopsies performed with C-BF depending on the target site: Adequate samples were respectively obtained in 96% (22/23) of specimens from the intrapancreatic common bile ducts, 92% (11/12) of those from the upper common bile ducts, 80% (12/15) from the carrefour of the hepatic ducts, 75% (9/12) from the right intrahepatic bile ducts, and 31% (5/16) from the left intrahepatic bile ducts.

Moreover, the diagnostic sensitivity for biliary strictures reported was just 60%, which is similar to those reported from studies carried out on conventional forceps biopsy. The benefits of using C-BF may be limited because of its lack of rotation torque ability; thus, only a curvature to the patient's right-hand side can be performed: This feature leads to an adequate sampling of lesions located to the right intrahepatic bile duct (75%), in contrast to a poor success rate in procedures that involved selecting the left intrahepatic bile duct (31%).

Another novel slim biopsy forceps, with a soft and thinner shaft of 1.8 mm (Radial Jaw 4P, Boston Scientific, Boston, MA, United States), has been developed to enable the jaws to pivot onto the targeted biopsy site for better tissue grasping. To evaluate the feasibility and efficacy of this novel biopsy device in the diagnosis of MBS, in 2017, Yamamoto *et al*[12] tested it on a cohort of 360 patients who underwent ERCP for biliary strictures. That study showed a higher sensitivity than previous studies of trans-papillary bile duct biopsies: In fact, the overall sensitivity and accuracy were 69.6% and 78.8%, respectively. The sensitivity was 75.6% in cholangiocarcinoma, 64% in pancreatic cancer, and 57.1% in metastasis. In cholangiocarcinoma, a lower sensitivity was observed for perihilar lesions (68.7%) rather than for distal stricture (83.1%). A better sensitivity has been reported for longer stenosis of pancreatic cancer and metastasis. These results suggest that trans-papillary forceps biopsy should be performed in consideration of the stricture level, stricture length, and cancer type. Actually, a lower sensitivity was observed for the perihilar MBS rather than for the distal one. This may be due to the features of the strictures: Narrow, smooth, and angled lesions could lower the biopsy forceps ability to hit the targeted area. Moreover, the distance of the MBS from the papilla could reduce the possibility of precisely grasping the lesion. In contrast, a better sensitivity was observed for the distal MBS. Regarding the lower bile duct, a better sensitivity was observed for the strictures in which an adequate space to open enough the biopsy forceps jaws was present.

In 2017, Kwon *et al*[13] reported a single experience of MBS sampling with the use of a custom-made prototype guide-wire assisted endobiliary forceps biopsy: Targeted sampling from the central area of the mass was easy and successful.

Peroral cholangioscopy

Peroral cholangioscopy (POCS) modalities provide direct visualization of the biliary ductal system. Those procedures are important diagnostic tools in cases of suspect MBS in which other available invasive/non-invasive imaging modalities (*e.g.*, EUS, CT, MRI, and ERCP with transpapillary biopsy sampling) cannot provide a definitive diagnosis. Three different cholangioscopic techniques are currently available: The "mother-baby" dual-operator cholangioscopy (DOC), the "mother-baby" single-operator cholangioscopy (SOC), and the direct cholangioscopy[14]. DOC is necessarily performed by two endoscopists with the use of a very slim endoscope passed through the working channel of a duodenoscope up to cannulating the common bile duct, usually over a guide-wire. POCS with optical image manipulation using narrow-band imaging (NBI) allows emphasizing the imaging of certain features of the bile duct tissue, such as mucosal structures and capillary vessels (*e.g.*, irregular and tortuous vessels, papillogranular or nodular elevated surface), enabling to target biopsy onto the suspect lesion.

A prospective multicentre study on indeterminate bile duct lesions and preoperative mucosal cancerous extension diagnosis by DOC plus NBI was conducted by Osanai *et al*[15] in 2013. This work was conducted on a cohort of 87 patients of whom only 35 underwent endobiliary forceps biopsy sampling *via* DOC for indeterminate lesions. In 34/35 patients, NBI was useful in differentiating benign from malignant lesions. Collected data showed an accuracy rate of 85.7 % for indeterminate biliary lesion diagnosis using endobiliary forceps biopsy *via* DOC. That study also reported additional accuracy for detection of mucosal cancerous extension in the bile duct with POCS: In fact, the accuracy rate of ERCP alone in verifying the presence or absence of mucosal cancerous extension was 73.5%, in comparison to an accuracy rate of 92.9% for ERCP with POCS plus biopsy. However, as the authors acknowledged, that prospective study had the same bias concerning the non-randomized selection of

patients and the fact that most of the targeted patients had already a bile duct cancer diagnosis: Those aspects could explain the high rate of accurate diagnosis of the study. A video endoscope and a disposable access catheter using fiberoptics (SpyGlass system; Boston Scientific, MA, United States) enable the SOC modality[16].

Since the launch of the first-generation SpyGlass system, in 2007, several studies have reported increasing sensitivity and accuracy with the addition of its direct endoscopic visualization of the bile duct to ERCP or tissue sampling [17-19]. However, the mean sensitivity of biliary sampling, using the dedicated biopsy forceps (SpyByte), for discriminating between malignant and benign biliary lesions was only slightly superior (68%) to that of the other conventional sampling modalities (Figure 2).

The initial version of SpyGlass was fiberoptic and the optical probe was reusable. Since 2015, a new digital single-operator/single-use instrument (SpyGlass DS; Boston Scientific, MA, United States) has been available. This 2nd generation system does not require to be reprocessed to avoid the issue of potential image degradation with repeated use. In 2016, a prospective multicenter study in Japan enrolled 148 patients with a collection of pancreaticobiliary diseases (124 with biliary disease). This work reported a SpyGlass targeted biopsy sensitivity of 81.4% and an accuracy of histologic diagnosis in indeterminate biliary strictures of 70.7%[20].

Direct cholangioscopy employing is questionable because of the same safety issue related to the occurrence of rare but life-threatening adverse events such as stroke caused by leakage of air into the portal or hepatic venous system[21], biliary perforation, and slightly higher incidence of postprocedural cholangitis[22].

Intraductal ultrasound-guided biopsy

IDUS involves the insertion into the bile duct of a high-frequency ultrasound ultrathin probe, generally over a wire. It provides high-resolution images of the ductal wall and periductal tissues[23]. Potentially, IDUS could be an important diagnostic tool in the evaluation of the indeterminate biliary strictures in whom is not possible to obtain a diagnosis despite previous evaluations. ERCP with IDUS examination, if performed by an expert endoscopist trained in both EUS and ERCP, helps to identify patients with a high suspicious of MBS[1] better than EUS does, particularly for lesions located at the hilum or mid-bile duct[23,24]. Several studies[25-28] reported high diagnostic sensitivity and specificity of IDUS during ERCP in differentiating malignant from benign strictures. Since IDUS provides real-time, high-resolution images of the bile duct wall and the adjacent structures[27], it is an ideal tool to use before biliary stenting. Unfortunately, this modality is not widely used because of the lack of ERCP operators who are also skilled in EUS. IDUS is also limited by the lack of a specific sampling modality.

Consequently, based on those aspects, two studies have investigated the performance of IDUS-guided biopsy sampling[29,30]. In these two works the ultrasonic probe is inserted into the bile duct over the wire after endoscopic sphincterotomy until IDUS recognize the suspected MBS. While maintaining the ultrasonic probe on the narrowest position to the stricture, a conventional biopsy forceps is inserted into the orifice of the papilla to the tip of the placed ultrasonic probe under fluoroscopic guidance. During the trans-papillary biopsy forceps sampling the scanning ultrasonic probe is keep at the nearest intraductal position.

Jong *et al*[29] reported a higher sensitivity for cancer diagnosis of indeterminate biliary strictures (87% with IDUS-guided biopsy in comparison to 67% with fluoroscopically trans-papillary guided biopsy).

Similarly, Kim *et al*[30] designed a prospective randomized study on the accuracy of IDUS-guided trans-papillary biopsy and conventional biopsy on fluoroscopy in suspected MBS and 65 out of 72 patients enrolled in the study underwent ERCP with IDUS.

The accuracy of IDUS-guided trans-papillary biopsy for MBS is significantly higher than conventional trans-papillary biopsy (90.8% *vs* 76.9%) in cases with intraductal infiltrating lesions, which were the most common findings on IDUS (47.5%). There was no significant difference in cancer detection rate according to the location of the stricture, as well as any significant improvement of cancer detection rates was reported in cases with extrinsic compressed lesions. This study reported no significant procedure-related adverse events (only two mild cases of hemobilia after trans-papillary forceps biopsy).

However, to date, there are no dedicated accessories that combine IDUS and forceps biopsy, thus IDUS-guided trans-papillary forceps biopsy is more challenging than conventional sampling modalities for the risks of bile-duct trauma. New types of IDUS probes or accessories for IDUS-guided trans-papillary forceps biopsy, as well as larger studies for validation, are expected.

Interventional radiology techniques

In cases in which the endoscopic approach to biliary strictures has failed or is deemed difficult or impossible due to unfavourable anatomy (*e.g.*, in cases of surgical interventions as hepatico-jejunostomy), their cyto-histological assessment can be performed with percutaneous transhepatic endobiliary brushing and/or forceps biopsy (PTEFB)[31].

Percutaneous transhepatic endobiliary sampling of biliary strictures/obstructions is usually performed after local anaesthesia and during conscious sedation, under fluoroscopic guidance, through a biliary drainage access, before drainage positioning, both from the right or left liver lobe based on stricture/obstruction location, even though right intercostal approach is preferred for positional

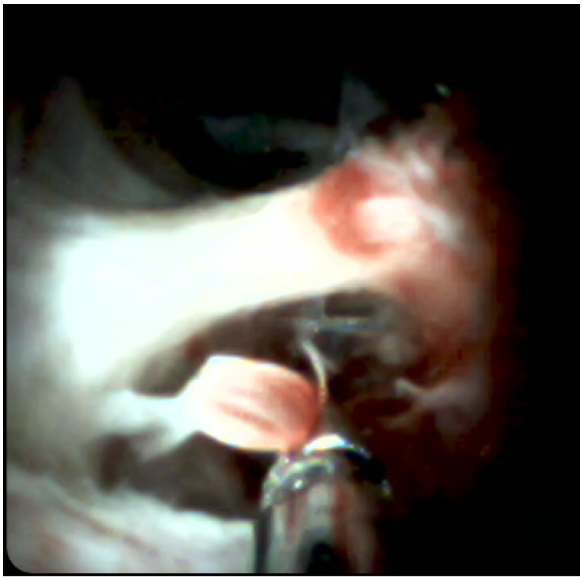

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Figure 2 Endobiliary biopsy performed using the dedicated biopsy forceps (SpyByte™), under PerOral Cholangioscopy.

advantage and operator easiness. Periprocedural broad-spectrum antibiotic coverage is recommended. In cases of occurrence of hemobilia or cholangitis after percutaneous transhepatic biliary access, the sampling should be delayed 24-48 h[32,33]. Cholangiography-guided detection of the stenosis/obstruction is obtained and, after passing through the stricture with a guide-wire and positioning a 6-8F introducer sheath in the biliary ducts, the sampling procedure can be performed.

In cases of brushing, a flexible probe with a brush on an atraumatic tip is introduced through the sheath up to the stricture and then is pushed and pulled and rotated under fluoroscopic guidance multiple times[34].

In case of PTEFB, a careful and accurate forceps biopsy is performed advancing the forceps through the introducer sheath. Patel *et al*[35] described a variant of this technique, the so-called "cross and push", in which the introducer sheath is advanced on a guidewire into the stricture/obstruction and is used to push the biopsy forceps granting greater stability of the forceps and allowing to obtain a larger lesion sample. Multiple samples should be taken, if possible, to obtain greater true-positive rates[36]. A bile sample after the brushing/biopsy (as much as 10 milliliters) should be always taken for bile cytology, as it demonstrated to have up to a 34% of sensitivity, which increases to 52% in case of multiple and seriate samplings[37,38]. In the case of forceps biopsy, a transhepatic cholangiography should be always performed to evaluate contrast medium leak from the bioptic site.

Cyto-histologic diagnosis of the sample obtained with the biopsy must always be confirmed after the surgical excision or, in case of benign disease diagnosis or non-specific findings, after dimensional stability of the lesion at a close follow-up. Redo-sampling should be performed in cases of a negative histological result, particularly in patients with high suspicion of malignancy, and in cases in which the operator deemed the first histological specimen inadequate for evaluation, as the fibrotic and scirrhous tissue which associates to cholangiocarcinoma and pancreatic carcinoma, in addition to necrotic and inflammatory changes, can hinder a correct diagnosis, even though Rabinovitz *et al*[436] reported that biopsies repeated three or more times yielding only negative results should reduce the probability of malignancy to 0%; it is mandatory, however, to perform a strict imaging and laboratory follow-up in these patients.

Percutaneous transhepatic endobiliary brushing demonstrates sensitivity rates ranging from 26 to 67%, and low negative predictive values (around 12.5%). Noticeably, Xing *et al*[39] reported a superior sensitivity value of 75% with greater sensitivity in cases of cholangiocarcinoma *vs* other strictures ($P < 0.05$) while stricture location had no effect on brushing sensitivity[32,34,40-43].

Overall percutaneous biliary forceps biopsy sensitivity has been attested between 55.8 and 93.3%, with a higher sensitivity for cholangiocarcinoma (up to 94%)[33,35,40,41,44-47]. Augustin *et al*[44] performed PTEFB in 13 patients, with at least 3 samples of 1-2 mm per patient, and in 92.3% of cases the material was deemed sufficient for histological analysis; PTEFB had sensitivity and accuracy rates of 88.9% and 92.3% respectively.

Jung *et al*[33] performed 130 PTEFB obtaining a 78.4% sensitivity rate. Park *et al*[48] retrospectively reviewed 271 PTEFB, finding 77.2% of sensitivity and 78.9% of accuracy. Patel *et al*[35] with their abovementioned "cross and push" technique performed in 52 patients obtained a sensitivity of 93.3%. Inchingolo *et al*[47] prospectively performed 30 PTEFB in 29 patients, with the "cross and push" technique, obtaining a sensitivity rate of 91.67% and an accuracy rate of 92.59%. Boos *et al*[40] described

better sensitivity rates when forceps biopsy and brush cytology were combined in a tandem approach (55.8% *vs* 40.6% of forceps biopsy alone); while this procedure can be considered expensive when compared to the use of forceps biopsy alone, it is cost-effective when compared to performing two separate procedures in case of an initial negative histological sample; however randomized studies comparing the sensitivity of the two approaches (single and tandem) should be performed. The tandem approach must be distinguished from obtaining a smear from forceps biopsy for cytological analysis [41].

PTEFB can be also performed under cholangioscopic/choledochoscopic guidance, which gives the operator the ability to directly visualize and target the pathologic tissue (Figure 3). After adequate sequential dilation of the transhepatic tract (with an introducer sheath of up to 11-16 F *vs* 7-8 F of fluoroscopy-guided PTEFB) a scope is positioned over a stiff guidewire and the forceps are inserted through its working channel. This approach has sensitivity and specificity exceeding 95% for diagnosing biliary malignancies despite its greater costs when compared to fluoroscopy-guided PTEFB and the need for specialized equipment and expertise[32,42,49,50]. Due to the diameter of the cholangioscope and the risk of hemobilia after first puncture of the biliary ducts, percutaneous tract "maturation" for one week or more after placement of a 8-10 French biliary drainage is recommended to avoid hemorrhage and prevent peritonitis due to extra-hepatic bile leak, as well as progressive oversizing of the biliary tube reduces the subsequent trauma from cholangioscope insertion[51]. Flexible endoscopes are preferred over the rigid ones due to their smaller diameter, better control and wider view; in addition, long endoscopes should be preferred, particularly in case of lesions in the distal common bile duct or in the contralateral ducts. Complication of transhepatic cholangioscopy include cholangitis, hemobilia, biloma or abscess formation, but in half of cases are related to the initial access and tract dilation, and can be avoidable with tract maturation[52].

Among percutaneous transhepatic biopsy approaches, Schechter *et al*[55] reported the use of the Simpson atherectomy catheter, with a sensitivity of 79% but 11% of hemorrhages, high costs, and difficulties in passing through angled transhepatic tracts.

On the other hand, Rossi *et al*[34] described the diagnostic yield of sampling the balloon surface in patients with strictures which needed bilioplasty, reporting a sensitivity of 87.5%.

Various authors reported great diagnostic sensitivity of PTEFB in strictures of the upper biliary tree (up to 92%), whereas Ierardi *et al*[56] reported lower sensitivity for lesions of the hilum and common bile duct as compared to the common hepatic bile duct and ampulla[33,35,42,54,55]. Overall, the PTEFB procedure does not have severe technical difficulties, therefore the learning curve is reported to be steep, with only a few cases needed to master the technique[47].

In terms of safety, PTEFB yielded low rates of complications, the most common being transient hemobilia, postprocedural cholangitis, transient bile leakage, and less often, the formation of biloma in the bioptic site, which were promptly treated with percutaneous drainage[33,35,44,45,47].

Other complications were related to the percutaneous puncture and not to the sampling procedure itself, ranging from subcapsular biloma to hepatic hematoma to pseudoaneurysm formation[35,56].

The main limitation of PTEFB is linked to the diagnosis of extra-biliary neoplasms determining biliary obstruction and which have not infiltrated yet the biliary duct walls (*e.g.*, hepatic hilum lymph-nodal metastasis, tumor infiltration/compression), due to the limited tissue samples, determining false-negative results both during surgical inspection or at follow-up[57]. Among metastatic tumor-related extrinsic biliary compression, the prospective analysis from Estrella *et al*[58] demonstrated that metastases from colorectal cancer more commonly present with intrabiliary growth when compared to other tumors (10.6 *vs* 1.9%). Another limitation is represented by the intrinsic characteristics of the forceps, which can cause "crush" artifacts of the bioptic specimen, represented by the degradation of the specimen during the bioptic maneuver, that can hinder the diagnosis[35].

Discussion

The diagnostic approach (Table 1) and correct histologic identification of a biliary stricture can be a demanding issue, while first-line non-invasive diagnostic methods alone cannot confirm the diagnosis of MBS in most of the cases. Moreover, pathological diagnosis is mandatory for the decision on the therapeutic approach. Therefore, it is crucial to establish the optimal sampling modality to confirm the diagnosis. According to current literature, both PTC and ERCP forceps biopsy are sensitive and accurate sampling modalities for suspected MBS.

Chang *et al*[45] retrospectively compared a group of 38 patients undergoing PTEFB and brushing with a group of patients undergoing endoscopic trans-papillary biopsy; PTEFB had a sensitivity of 86.7% compared to the 77.1% of endoscopic biopsy, especially for biliary strictures located at the hilum. Mohkam *et al*[46] retrospectively compared 75 PTEFB with patients who underwent endoscopic trans-papillary biopsy and PTEFB demonstrated sensitivity rate of 69%, similar to endoscopic biopsy (75%, P = 0.45). The choice of biliary strictures that more suitable for endoscopic rather than a percutaneous biopsy seems to mainly depend on the anatomical location and type of stricture.

Several studies[45,54] demonstrated that PTEFB is correlated with high diagnostic sensitivity for strictures located in the upper biliary tree, distant from the papilla – where endoscopic biopsy has better sensitivity. Particularly, Chang *et al*[45], reported higher sensitivity for PTEFB in hilum lesions than those located within the common bile duct. According to the authors, sensitivity was higher for

Table 1 Tools for endobiliary biopsy sampling

Endoscopic techniques		
	Advantage	Disadvantage
ERC + TPB	Safeness, feasibility and large availability; better sensibility for MBS versus brushing	Low sensitivity for MBS (48%), difficulty of cannulation with standard biopsy forceps, not easy targeting of the lesion
ERC + TPB with C-BF	Slight better sensibility (60%) for MBS respect to conventional biopsy forceps	Sampling benefits limited to lesions located to the right intrahepatic bile duct (75%)
Cholangioscopy + endobiliary biopsy	Gain in accuracy for diagnosis of malignancy in indeterminate lesions (85-92%) versus ERCP + TPB	Same safety; issue with direct cholangioscopy related to rare adv events (leakege of air in to portal vein)
IDUS + TPB	Higher sensitivity for malignancy in indeterminate intraductal lesiones (87-91%) versus ERCP + TPB	Advanced experience in both ERCP/EUS requested, lack of standardized procedure and specific devices, time-consuming technique
Interventional radiology techniques		
	Advantage	Disadvantage
PTE endobiliary brushing	Safe, cheap and large availability;	Low sensitivity for MBS
PTE endobiliary biopsy	High sensitivity; Larger biopsy cup comapred to ERC + TPB	Indirect visualization of the lesion
Colangioscopy + PTEFB	Direct visualization of the lesion;	Combined procedure with endoscopist; Expensive procedure; small size specimen

TPB: Trans papillary biopsy; IDUS: Intraductal ultrasound; ERC: Endoscopic retrograde cholangiography; PTEFB: Percutaneous transhepatic endobiliary brushing and/or forceps biopsy; C-BF: Controllable biopsy-forceps; EUS: Endoscopic ultrasonography.

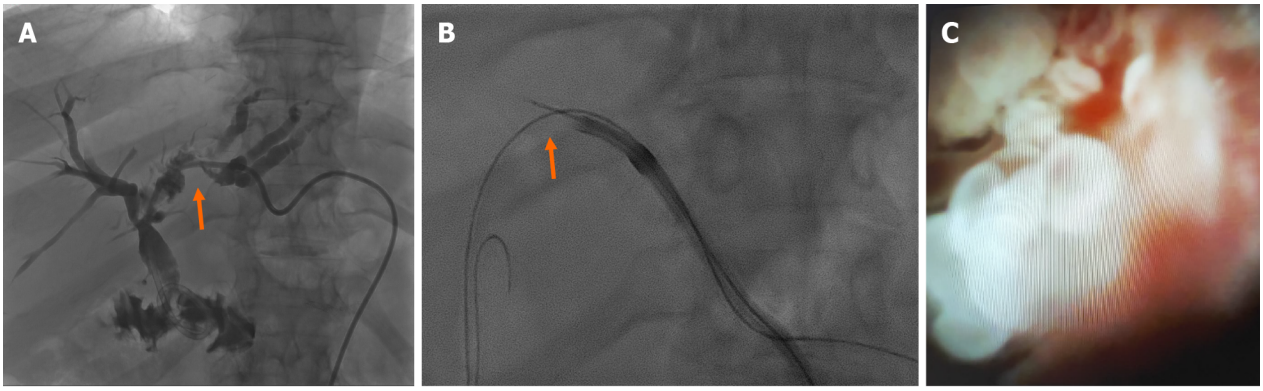

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Figure 3 Endobiliary biopsy performed using the dedicated biopsy forceps (SpyByte™), under Perctaneous Cholangioscopy. A 63 year female, with history of Whipple's procedure 20 years before. A: Cholangiography revealed multiple endoluminal defects (red arrow); B: Endobiliary biopsy using SpyByte, under fluoroscopy and cholangioscopy; C: Histological examination revealed intestinal metaplasia of the biliary mucosa.

strictures located close to the hilum. On the contrary, compared to PTC, ERCP resulted in higher accuracy for lower strictures. In this setting, the distance between the site of biliary stricture and the device used to push and maneuver the biopsy forceps seems to play a key role: the greater the distance, the lesser the precision of sampling. Therefore, specimen sampling of the biliary strictures located proximal to the hilum should ideally be performed *via* PTEFB, while for strictures located at the hilum or more distally, ERCP should be preferred. Other factors influencing the effectiveness of endobiliary biopsy are insufficient space for forceps opening noted in cases of severe strictures, lesions located at sites with marked angulation, lesion shape, and of course local expertise, and device availability.

CONCLUSION

Both ERCP and PTC endobiliary biopsy remain valid methods for tissue identification demonstrating satisfactory diagnostic accuracy, especially in properly selected lesions. Novel slim biopsy forceps and new endobiliary sampling modalities such as POCS, and IDUS-guided biopsy, currently under investigation, seem to improve the efficacy of histologic characterization.

FOOTNOTES

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MINIREVIEWS

Lessons learned: Preventable misses and near-misses of endoscopic procedures

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Abstract

Endoscopy is a complex procedure that requires advanced training and a highly skilled practitioner. The advances in the field of endoscopy have made it an invaluable diagnostic tool, but the procedure remains provider dependent. The quality of endoscopy may vary from provider to provider and, as a result, is not perfect. Consequently, 11.3% of upper gastrointestinal neoplasms are missed on the initial upper endoscopy and 2.1%-5.9% of colorectal polyps or cancers are missed on colonoscopy. Pathology is overlooked if endoscopic exam is not done carefully, bypassing proper visualization of the scope's entry and exit points or, if exam is not taken to completion, not visualizing the most distal bowel segments. We hope to shed light on this issue, establish areas of weakness, and propose possible solutions and preventative measures.

Key Words: High-quality colonoscopy; Esophagogastroduodenoscopy; EGD; Cancer screening; endoscopy; Missed lesions

Core Tip: Endoscopy has become a widely used diagnostic tool and plays an instrumental role in screening and surveillance of gastrointestinal pathology. Despite its wide acceptance, it remains provider dependents and, as a result, is not perfect. Both upper and lower endoscopy have weaknesses and shortcomings unless executed flawlessly. A high-quality endoscopy includes a complete examination of the bowel, including distal segments that are difficult to visualize, as well as scope's entry and exit points. Better understanding of the shortcomings of endoscopy may help change training and improve physician awareness.

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INTRODUCTION

Today, endoscopy is considered one of the best diagnostic tools for screening and surveillance of gastrointestinal pathology. Since the beginning of the 21st century, endoscopy use has risen by more than 50%[1]. With wider utilization of endoscopy, it has become more and more evident that the procedure quality is multifactorial and operator dependent[2]. Consequently, lesions may be missed depending on the level of provider training, procedural skills, and attentiveness to subtle pathology. This prompted development of several quality metrics to provide guidance for operators[3-7]. Despite proposed quality metrics, there is still a significant number of missed gastrointestinal cancers. A meta-analysis by Menon *et al*[8] suggested that 11.3% of upper gastrointestinal (UGI) neoplasms are overlooked on the initial upper endoscopy (EGD). Around 2.1%-5.9% of colorectal polyps or cancers are missed on colonoscopy[9]. The difference likely stems from the fact that endoscopic training has historically put emphasis on colorectal cancer prevention and screening, while there is usually less awareness around UGI neoplasms.

It should be noted that aside from neoplastic lesions, bleeding sources can be missed on endoscopy and only seen on repeat examination in patients with unexplained occult GI bleed or iron deficiency anemia with negative diagnostic work up[10]. Missed lesions on endoscopy are a common reason for malpractice lawsuits[11], which further emphasizes the importance of quality improvement. Some of the common reasons for why pathology is overlooked are a hastily performed endoscopy that bypasses proper visualization of the scope's entry and exit points, not taking endoscopic exam to completion, and not visualizing more distal bowel segments.

REVIEW

Using our personal experience with 4 patients who had lesions missed or near missed on endoscopy, we hope to expose some of the weaknesses and shortcomings of endoscopy. Our goal is to bring the attention of other gastroenterologists to these commonly missed areas that may go undetected.

Case 1

The first patient was a 72-year-old male who presented with symptoms of dysphagia. The initial EGD was unrevealing. It was only after the second EGD that a flat squamous cell carcinoma was appreciated 2 cm below the upper esophageal sphincter (UES) (Figure 1A, Figure 2A). The lesion was missed on the initial scope insertion and was likely missed because of a rapid scope withdrawal.

Case 2

The second patient was a 40-year-old female with iron deficiency anemia requiring multiple blood transfusions. The patient had undergone multiple upper and lower endoscopies and a capsule study, all of which were unrevealing. It was only after the 4th portion of the duodenum was examined that a malignant gastrointestinal stromal tumor was identified, diagnosed, and resected (Figures 1B and 2B).

Case 3

The third patient was a 50-year-old female who presented with ongoing diarrhea. Stool studies revealed cryptosporidium. Fortunately, the patient's colonoscopy included examination of the terminal ileum and was able to detect a small submucosal carcinoid tumor (Figures 1C and 2C). It was successfully resected with metastatic disease noted in only one lymph node.

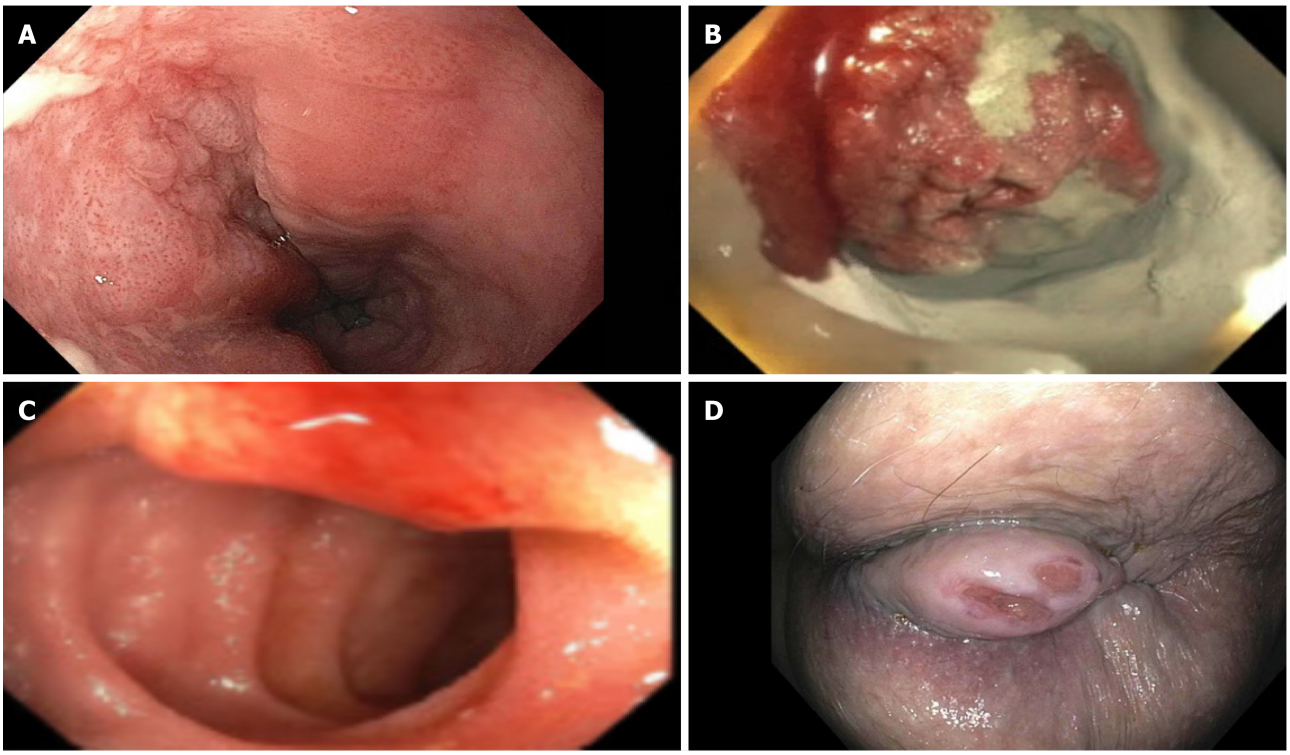

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Figure 1 Endoscopic visualization of the lesions near missed. A: Subtle flat squamous cell carcinoma was appreciated 2 cm below the upper esophageal sphincter; B: Malignant gastrointestinal stromal tumor treated with hemospray in proximal jejunum; C: Small submucosal carcinoid tumor in terminal ileum; D: 2 cm anal squamous cell cancer noted on rectal exam.

Case 4

Our last patient was a 68-year-old with a history of cirrhosis and recurrent bright red blood per rectum. She had 2 colonoscopies done to find the bleeding source, both were unrevealing. It was months later that the patient had a 2 cm anal growth examined and diagnosed on careful retroflexion. The anal lesion was then seen on a reinspection of the anal area. (Figures 1D and 2D).

DISCUSSION

Increasing awareness of the bowel segments at risk for being missed on endoscopy is important. Similarly, it is important to incorporate technical maneuvers that could help identify these challenging lesions into fellowship training and post-graduate courses to help practicing endoscopists (Tables 1 and 2)[10]. Lastly, following the most recent endoscopy quality metrics will help improve the detection of challenging lesions.

Colonoscopy

A complete colonoscopy should include a thorough exam of the endoscope's entry point (anal canal), all segments of the colon, and, if possible, the distal ileum. We are going to discuss distal to proximal bowel segments as visualized on colonoscopy and use it as a framework to go over commonly missed lesions for each segment along with maneuvers and techniques that can help detect them.

Anorectum: Some of the commonly missed lesions in anorectum are anal and rectal cancer, anal fissures, recto cutaneous fistulas, anal warts (Table 1)[10]. This is likely because of the scopes entry point being overlooked or not property visualized at the beginning of the procedure. The importance of anal examination by a skilled endoscopist if further emphasized by the fact that anorectal lesions can have a non-specific presentation and may go undiagnosed by patient's primary care physician. Chiu *et al*[12] found that only 54% of patients have a rectal examination by their primary care provider when they present with a non-specific anal complaint. Another study indicated that only 23% of patients presenting with anal complaint were diagnosed correctly by their primary care provider; the remaining patients were erroneously diagnosed with hemorrhoids[13]. As a result, this leads to delay in diagnosis and management of anal and rectal cancers. As proposed by quality metrics, digital rectal exam needs to be performed and thoroughly documented prior to colonoscopy (Table 2)[11]. Another maneuver that

Table 1 Commonly missed lesions requiring second-look colonoscopy[10,14-16] or upper endoscopy[10,20,24]

Bowel segment	Lesions missed	Intervention to improve lesion detection
Anorectum	Anal/rectal cancers	Careful anorectal exam before and on scope insertion with retroflexion
	Anal fissures	
	Recto-cutaneous fistulas	
	Anal warts	
Colon	Lesions in colonic folds (particularly sigmoid)	Careful exam between the folds of the colon, especially in sigmoid segment, consider using a cap
		Excellent, good, or adequate bowel preparation, supported by photography
	Right colon	Second look
		Retroflex in right colon
	Cecum (especially behind IC valve)	Document examination
		Examine behind the ileocecal valve
		Cecal intubation rate
Terminal ileum	Lesions in ileum	Intubate in the terminal ileum
Esophagus	Below UES lesions, *i.e.*, squamous cell carcinoma	Careful examination of upper esophagus, slow scope withdrawal
	Distal esophagus, collapsed varices in volume depleted patient	Careful examination of distal esophagus and awareness of patient's volume status
	Subtle lesions of Barrett segment	Adequate time for examination of the segment
Stomach	Cameron lesions, gastro-esophageal junction (especially challenging to detect/examine with large hiatal hernias)	Careful examination of gastro-esophageal junction and diaphragmatic hiatus with retroflexion of the scope
	Arteriovenous malformation, Dieulafoy's lesions	Careful inspection between the gastric folds using a cap
Small bowel	Duodenal bulb	Examine all 4 walls of the duodenal bulb and
	Duodenal sweep	May need to use of a side view scope
	3rd and 4th part of the duodenum	Advance scope by reducing the loop into 3rd and 4th parts of duodenum

UES: Upper esophageal sphincter.

could be used to enhance detection of challenging lesions in anorectum is retroflexion. It allows for a better visualization of distal rectum and distal anus (Table 1)[14]. Retroflexion needs to be photographed and documented[11].

Colon: Some of the commonly missed lesion of colonic segment include lesions found inside the colonic folds (especially in sigmoid colon), right-sided colon, cecum [especially behind the ileocecal (IC) valve], and distal ileum (Table 1). There are a few techniques that can be implemented to facilitate detection of these challenging lesions (Table 1). Endoscopists should do a thorough examination between the haustral folds to avoid missing even large polyps that can hide inside the folds. Cap-assisted colonoscopy is another acceptable option as it involves a transparent attachment at the end of the scope that can improve adenoma detection rate (ADR) by flattening of the haustral folds and improving visualization of mucosa, especially on scope withdrawal[15].

Second look examination of the right side of the colon can help reduce the rate of cecal lesions missed [16]. Retroflexion in the right colon is another maneuver that can enhance visualization of right-sided lesions and improve ADR[14,16]. It entails bending of the scope in a *U*-turn such that viewing lens is facing backwards[14].

Cecum intubation is a very important skill and a quality measure that can enhance visualization of the cecum and identify lesions that are oftentimes missed. Additionally, endoscopists should pay particular attention to the mucosa behind the IC valve. Documentation of cecal landmarks is crucial.

All maneuvers discussed need to be thoroughly photographed and documented in the procedure description per the colonoscopy quality metrics (Table 2). Quality metrics further require bowel preparation to be excellent, good, or adequate and supported by photography and withdrawal time

Table 2 Quality metrics for endoscopic procedures[11,20,21,23,24]

Colonoscopy	EGD
High quality bowel preparation (excellent, good, or adequate), documented with photos	At least 1 min of inspection per centimeter of circumferential segment of Barrett's esophagus
Digital rectal examination prior to colonoscopy with results documented	NDR record should be considered
	When evaluating for gastric intestinal metaplasia, 5 or more biopsies need to be taken
Cecal intubation performed, landmarks noted in documentation and photos recorded	Overall, EGD evaluation for gastric intestinal metaplasia has to last 7 min or more
Withdrawal time is 6 min or more	
Retroflexion, if performed, is thoroughly documented (with photographs)	
Endoscopists ADR exceeds recommended thresholds. Physician participates in quality-improvement and continues to measure individual ADR	

EGD: Endoscopy; NDR: Neoplasia detection rate; ADR: Adenoma detection rate.

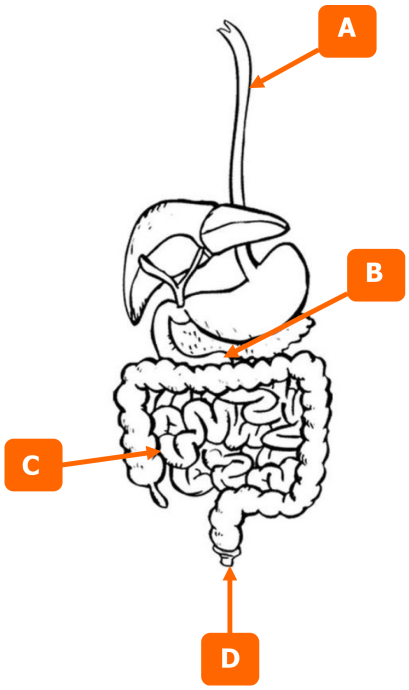

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Figure 2 Gastrointestinal tract segments at risk for having lesions missed. A: Upper esophageal sphincter; B: Proximal jejunum; C: Terminal ileum; D: Anus.

should be noted in documentation and exceed 6 minutes[11]. It is also encouraged that practicing endoscopist's adenoma detection rate (ADR) exceeds recommended thresholds. Physicians should routinely measure their ADR and participate in quality improvement programs[11].

The optimal withdrawal time for colonoscopy remains an important topic. A 6-minute withdrawal time was accepted, but a recent meta-analysis by Bhurwal *et al*[17] of 69551 patients compared withdrawal time of 6 *vs* 9 min in its ability to detect adenomas. They found that odds ratio for ADR was significantly higher at 1.54 for colonoscopies with withdrawal time of 9 min or more[17].

Terminal ileum: Lesions can be missed in terminal ileum as many colonoscopies do not investigate this bowel segment. It is important to note that the ileum is the most common site for development of carcinoid tumors (57%) and that even primary ileal tumors are missed on computer tomography (CT) scans in 64% of cases[18-20].This emphasizes the importance of a thorough and complete endoscopic exam that may detect primary ileal tumors early and allow for timely intervention[20]. Endoscopists should try to intubate the terminal ileum whenever feasible.

Upper endoscopy

A complete EGD should entail a thorough exam of the esophagus, including the UES, point of entry into the stomach, other poorly visualized areas of the stomach, along with all segments of the duodenum. We are going to discuss distal to proximal bowel segments as visualized on EGD and use it as a framework to go over commonly missed lesions for each segment along with maneuvers and techniques to help detect them.

Esophagus: Some of the most commonly missed esophageal lesions are immediately below the UES and lesions in the distal esophagus (such as collapsed varices in a volume depleted patient or subtle changes of Barrett's segment) (Table 1)[10]. Some possible interventions to facilitate detection of challenging lesions are careful examination of the full length esophagus paying particular attention to upper and lower most segments, being aware of patient's volume status, and allotting adequate time for examination of the segment (Table 1). Quality metrics for Barrett's segment inspection time call for 1 minute inspection time per cm of circumferential length[21]. Longer inspection time results in a more careful visualization of the mucosa and subsequently increase chances of detecting pathology[21]. Another quality metric that is being proposed when examining esophagus is neoplasia detection rate (NDR)[22]. Like ADR for colonoscopy, it is important to keep track of NDR for EGD when examining for Barrett's segment, because it reflects the quality of inspection[22].

Stomach: Some of the common gastric lesions missed on EGD are Cameron lesions, lesions around gastro-esophageal (GE) junction (especially with large hiatal hernias), arteriovenous malformations, Dieulafoy lesions (Table 1). Some interventions that can be done are careful inspection of GE and diaphragmatic hiatus with retroflexion of the scope, inspection between gastric folds using the previously discussed cap-assisted endoscopy (Table 1)[23]. One of the EGD quality metrics that is important to remember is adequate number of gastric biopsies, which should be greater or equal to 5 [24]. Timing is another important quality metric. Examination time during EGD when looking for intestinal metaplasia should be longer than 7 min, because longer inspection implies a more careful exam and results in a higher rate of neoplasia detection[25]. Park *et al*[25] observed that slow endoscopists (defined as withdrawal time of more than 3 min) were better at detecting neoplastic lesions (0.28%) compared to fast endoscopists (0.20%). As a result, they proposed that examination time could be a surrogate measure for the procedure quality[25]. Another study identified that endoscopist who takes more than 7 min to complete exams is more likely to detect a high-risk gastric lesion when compared to a fast endoscopist[26]. Given heterogeneity of data between the two studies, it is difficult to draw conclusions regarding the optimal examination time. This is further complicated by the fact that longer endoscopic times are associated with cardiac arrythmias, esophageal tears, aspiration, and bacterial translocation[27].

Incidence of gastric pathology varies in different countries. There is higher prevalence of gastric cancer in Eastern countries. Consequently, this led to increased awareness of gastric lesions and a more robust screening protocols in countries like Japan[28]. In Japan, it is recommended to undergo annual upper endoscopy for anybody over the age 40. As a result, there are more early-stage gastric lesions (53%) identified when compared to United States (27%)[29,30]. This shows that increased awareness and adequate training can improve subtle lesion detection.

Duodenum

Some of the commonly missed segments of the small bowel are duodenal bulb, duodenal sweep, and 3rd and 4th parts of the duodenum (Table 1). Some of the maneuvers that can help detect these challenging lesions are careful examination of all 4 walls of the duodenal bulb, use of a side view scope for the duodenal sweep, advancement of the scope by reducing the loop into the 3rd and 4th parts of duodenum (Table 1). Many upper endoscopies do not go past the 2nd part of the duodenum. Lesions in more distal segments of the duodenum (3rd and 4th) are usually more challenging to visualize and require an extra-long fiber optic scope and a trained endoscopist[31]. Interestingly, 60% of benign duodenal lesions and 50% of malignant duodenal lesions are only diagnosed on autopsy and missed on the endoscopic exam [32].

TRAINING

As we learn more about common pitfalls and shortcomings of endoscopy, training fellows to recognize them becomes the next key step. It is important to standardize best practices and shed light on the areas commonly missed in colonoscopy training[33]. One of the studies even suggested that pre-fellowship exposure to best practices of endoscopy, can improve the learning period and procedural skill of fellows [34].

ARTIFICIAL INTELLIGENT in ENDOSCOPY

Endoscopy continues to be an operator dependent procedure. As such, it presents a growing opportunity for development of machine learning technology and computer algorithms to assist endoscopists with lesion detection. Artificial intelligent (AI) has a promise to improve accuracy of endoscopic procedures, reduce inter-operator variability, and compensate for human error and factors contributing to it such as fatigue or limited experience[35]. Thus far, computer-aided detection algorithms of AI have been trained to detect lesions both macroscopically and by optical biopsy/microscopically[36]. Recent studies demonstrated that AI performed better than endoscopists in esophageal cancer and neoplasm detection in pooled sensitivity 94% *vs* 82%, respectively[37]. The specificity of AI-based endoscopy had specificity of 85% for esophageal cancer and neoplasms[37]. AI-based endoscopy provided a 26.5% increase in sensitivity for detection of early gastric cancer when compared to endoscopists (sensitivity of 95%)[38]. The specificity of AI-based endoscopy had specificity of 87.3% for early gastric cancer[38]. AI algorithms have also been targeted towards colorectal cancer detection. Recent reports suggest that AI-assisted colonoscopy has sensitivity of 94% [39,40]. While some reports suggest that AI may not show significant improvement in larger polyp detection rate (38.8% *vs* 26.2%), AI-based colonoscopy showed significant improvement in detection of small and flat polyps that are easily missed (76.0% *vs* 68.8% and 5.9% *vs* 3.3%, respectively)[41].

CONCLUSION

Endoscopy has developed into a sophisticated diagnostic tool that provides great accuracy in lesion detection, but it is not perfect and remains operator dependent. The cases we presented expose weaknesses and shortcomings of endoscopic examination for both the upper and lower gastrointestinal tract, providing an opportunity for improvement. Commonly missed areas and the reason for why they were missed need to be communicated to currently practicing gastroenterologists. Additionally, educating fellows during their training on the possible shortcomings and weaknesses of endoscopy may help improve the quality of procedures in the future.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Recognition of esophagitis in endoscopic images using transfer learning

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Abstract

BACKGROUND

Esophagitis is an inflammatory and damaging process of the esophageal mucosa, which is confirmed by endoscopic visualization and may, in extreme cases, result in stenosis, fistulization and esophageal perforation. The use of deep learning (a field of artificial intelligence) techniques can be considered to determine the presence of esophageal lesions compatible with esophagitis.

AIM

To develop, using transfer learning, a deep neural network model to recognize the presence of esophagitis in endoscopic images.

METHODS

Endoscopic images of 1932 patients with a diagnosis of esophagitis and 1663 patients without any pathological diagnosis provenient from the KSAVIR and HyperKSAVIR datasets were splitted in training (80%) and test (20%) and used to develop and evaluate a binary deep learning classifier built using the DenseNet-201 architecture, a densely connected convolutional network, with weights pretrained on the ImageNet image set and fine-tuned during training. The classifier model performance was evaluated in the test set according to accuracy, sensitivity, specificity and area under the receiver operating characteristic curve (AUC).

RESULTS

The model was trained using Adam optimizer with a learning rate of 0.0001 and applying binary cross entropy loss function. In the test set (n = 719), the classifier achieved 93.32% accuracy, 93.18% sensitivity, 93.46% specificity and a 0.96 AUC. Heatmaps for spatial predictive relevance in esophagitis endoscopic images from

the test set were also plotted. In face of the obtained results, the use of dense convolutional neural networks with pretrained and fine-tuned weights proves to be a good strategy for predictive modeling for esophagitis recognition in endoscopic images. In addition, adopting the classification approach combined with the subsequent plotting of heat maps associated with the classificatory decision gives greater explainability to the model.

CONCLUSION
It is opportune to raise new studies involving transfer learning for the analysis of endoscopic images, aiming to improve, validate and disseminate its use for clinical practice.

Key Words: Esophagitis; Endoscopy; Artificial intelligence; Deep learning; Transfer learning

Core Tip: Considering the clinical relevance of esophagitis, we proposed a deep learning model for its diagnosis from endoscopic images of the Z-line, *via* binary classification of the images according to the presence or absence of esophageal inflammation signs. The excellent accuracy and area under the receiver operating characteristic curve achieved demonstrate the potential of the adopted strategy, consisting of the conjunction of densely connected neural networks and transfer learning. With this, we contribute to the improvement and methodological advancement in the development of automated diagnostic tools for the disease, which reveal great potential in optimizing the management of these patients.

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INTRODUCTION

Esophagitis is an inflammatory and damaging process of the esophageal mucosa, that can be the outcome of different pathological processes, which share, however, the same clinical presentation: retrosternal pain, dysphagia, odynophagia and heartburn[1,2]. Different pathological processes may lead to esophagitis, with possible etiologies embracing gastroesophageal reflux disease (GERD), infectious processes, in eosinophilic esophagitis, medications or even radiation. In extreme cases, it can result in stenosis, fistulization and esophageal perforation[3]. These complications, however, may be prevented with precoce diagnosis.

Esophagitis can be suspected based on the clinical history, with a confirmation performed through endoscopic visualization. The differentiation of its etiopathogenesis may be determined from endoscopic and histological study of the esophagus. The endoscopic presentation of eosinophilic esophagitis is characterized by exudates, strictures and concentric rings. In colonization by *Candida sp.* there are small and diffuse yellow-white plaques; in cytomegalovirus infection there are large ulcerations; Herpes Virus, in turn, may cause multiple small ulcerations[3-5]. GERD, on the other hand, has a better-defined endoscopic classification with the Los Angeles classification, which has four gradations based on the presence, size and distribution of esophageal[6].

Machine learning, main exponent of artificial intelligence, has gained space and attention in healthcare and medical research, especially after the development and validation by Beam and Kohane [7] and Gulshan *et al*[8] of a deep learning algorithm capable of detecting the presence of diabetic retinopathy in studies of the retina[7,8]. In the context of esophagitis, the use of machine learning, especially deep learning, may be considered to determine, among others, the presence of esophageal lesions compatible with esophagitis.

Deep learning - which comprehends deep artificial neural network-based algorithms capable of learning from large amounts of data - is considered the state of the art in the field of artificial intelligence for computer vision[9]. Among the possible uses of such applications, there is the binary classification of images according to the presence or absence of a given finding. In these cases, a dataset comprising examples of the image type to be classified is divided into two distinct subsets: one to train the model (from which the weights will be learned) and the other to evaluate its performance[10]. It is important that the two subsets obtained are representative, in terms of labels proportion, of the original dataset.

Traditionally, algorithms for deep learning use large volumes of data for training. However, obtaining databases large enough to accurately train them can prove to be a highly expensive process. As a way of mitigating this situation, one can choose to apply a technique called transfer learning, which is based on the use of external data to perform a training step mentioned above[10]. The use of this technique makes it possible to obtain a scale of pretrained weights in computational models for analyzing, among others, medical images. It should be noted, however, that the use of pretrained weights does not exempt the need to carry out a training stage with data that are representative of the base to be tested, with this second training step (called fine tuning) aiming to improve, principally, the deep layers of the algorithm in order to obtain results with greater accuracy[11].

This study aims to develop a supervised deep learning model using a fine-tuned transfer learning dense convolutional neural network (DCNN) to recognize, in a binary way, the presence of changes compatible with esophagitis in images from endoscopic studies. Thus, it seeks to contribute to the advancement and methodological improvement of a cost-effective and accurate automated technology for the diagnosis of esophagitis, optimizing the management of patients who present this condition.

MATERIALS AND METHODS

Data acquisition

Endoscopic images of 1932 patients with a diagnosis of esophagitis and 1663 patients without any pathological diagnosis (in both cases being z line the image topography) were obtained from the publicly available KSAVIR Dataset[12] and HyperKSAVIR Dataset[13]. Were included in this study the images in both datasets labeled as "normal z line" and the images labeled as "esophagitis". From these data, we set out to develop a binary deep learning classifier using the DenseNet-201 architecture, a densely connected convolutional network which connects each layer to every other layer in a feed-forward fashion[14], pretrained on the ImageNet image set.

The top layer of the DenseNet-201 architecture was not included in our model, and its output (that is, the output of the final convolutional block) was converted from a 4 dimensional to a 2 dimensional tensor using global average pooling. As the final layer, we added a dense layer with one unit and sigmoid activation. The structure of the final deep neural network predictive model is summarized in Table 1, and its architecture is illustrated in Figure 1.

Model development, training, and validation

For this purpose, the images were converted to arrays of dimension 256 × 305 × 3, whose units were rescaled using the *densenet* preprocessor, and divided into training set (80%) and test set (20%). The training set (n = 2876) was divided in batches of size 16 and used to train, throughout 80 epochs, the transfer learning based neural network whose structure is shown in Table 1. The test set (n = 719) was used to evaluate the model according to the following metrics: accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC).

The adopted methodology is schematically summarized in Figure 2. All steps of the predictive model development were performed in Python (version 3.6.9), using Keras library.

Ethical disclosure

As previously stated, all the imaging data was obtained from the public datasets KSAVIR Dataset[12] and HyperKSAVIR Dataset[13] that were released for both educational and research purposes. Therefore, it was not necessary to submit this study to the ethics committee, being in accordance with all the established precepts by the Committee on Publication Ethics.

RESULTS

The model was trained using Adam optimizer with a learning rate of 0.0001 and applying binary cross entropy loss function. All layers of the DenseNet architecture incorporated in the model were set as trainable (that is, we fine-tuned all weights).

In the test set, which was designated to model evaluation, the classifier achieved 93.32% accuracy, 93.18% sensitivity, 93.46% specificity and a 0.96 AUC. The confusion matrix between true labels and labels predicted by the model is presented in Figure 3, while its receiver operating characteristic curve is presented in Figure 4.

In order to identify the imagery aspects related to the predictive decision, it is possible to plot heatmaps that indicate, colorimetrically, the areas with the greatest influence on the prediction. Examples of such heatmaps for esophagitis images contained in the test set are shown in Figure 5.

Table 1 Synthesis of the model's structure

Type of layer	Brief description	Number of parameters
Functional	Instantiates the DenseNet-201 architecture with average pooling of the output	18321984
Dense	One unit with sigmoid activation	1921

The functional layer instantiates the DenseNet-201 architecture, thus aggregating all its layers. The dense layer outputs the final binary classification of the model.

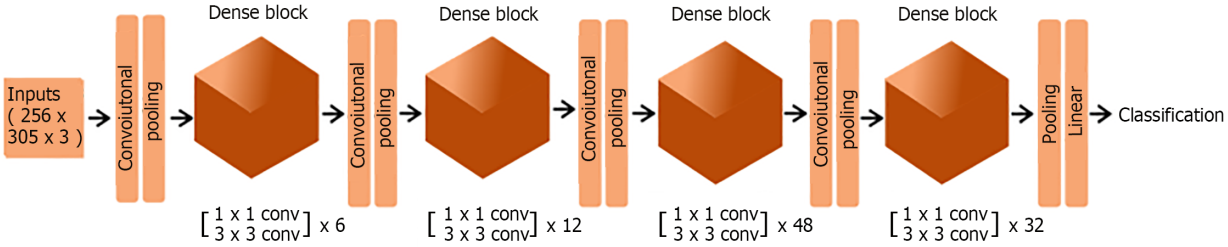

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Figure 1 Representation of model's final architecture. In the proposed model, each image is used as an input for a deep neural network composed of four blocks of densely connected convolutional layers, together with convolutional and pooling transition layers. The network output is a binary classification.

DISCUSSION

This study understands that transfer learning associated with DCNN has great potential to aid and improve the quality and rate of esophagitis diagnosis through endoscopic imaging. Improving workflow, providing faster preliminary reports, relieving the burden of the increasing patient population associated with the intensive and repetitive mechanical work is some of the promises of the integration of CNN-based algorithms to medical practice[15].

Once the mark of at least 93% in the parameters of accuracy, sensitivity, and specificity has been reached, we were able to demonstrate the potential of these algorithms to assist in the premature recognition of pathological predecessor endoscopic abnormalities, and as a consequence, to intervene positively in the management of these. Thus, the use of DCNN with pretrained and fine-tuned weights proves to be a good strategy for predictive modeling of this type (and potentially other types) of medical images. In addition, adopting the classification approach combined with the subsequent plotting of heat maps associated with the classificatory decision gives greater explainability to the model.

In consistency with findings described by Wimmer *et al*[16], when they established the potential of the association of transfer learning with CNN in the classification of endoscopic images, previously used focused on celiac disease, or also described by Song *et al*[17] when they reported a deep learning-based model with the ability to histologically classify polyps with a higher accuracy than trained endoscopists, the performance of our algorithmic model reaffirms the potential of deep learning for computer vision in the field of gastrointestinal diagnostics. In line with the mentioned studies, our study demonstrates the already defended potential of CNN-based artificial intelligence systems to diagnose esophageal disease, and can contribute with methodological insights for the development and improvement of such systems[18].

By recognizing changes in the mucosa of the esophageal Z-line, the binary transfer learning classifier presented in this study aims to demonstrate the effectiveness of these algorithms to differentiate endoscopic images of the same topography with and without changes characteristic of esophagitis. Unlike other studies that aimed at automatic detection of anatomical landmarks and diverse diseases affecting different anatomical sites using the KVASIR database[19-22], we employed state-of-the-art deep learning to specifically target Z-line related changes, bringing great accuracy to its analysis.

However, as it is well settled in applications of deep learning in medical image analytics[23], a major limitation of the technical capability of the proposed classifier is the lack of large-scale labeled data. As already shown by Sun *et al*[24], the performance on artificial intelligence in visual tasks increases logarithmically based on volume of training data size. Coupled with this factor, we cannot ensure how the binary classifier would behave in patients with the presence of other diseases. In both cases, however, training on more plural datasets should optimize performance on the parameters evaluated.

Concerning the predictive behavior towards other possible esophageal Z-line abnormalities, assuming that the algorithm was able to differentiate with high accuracy normal images from images with different degrees of inflammation - and consequently different mucosal lesion configurations - it is

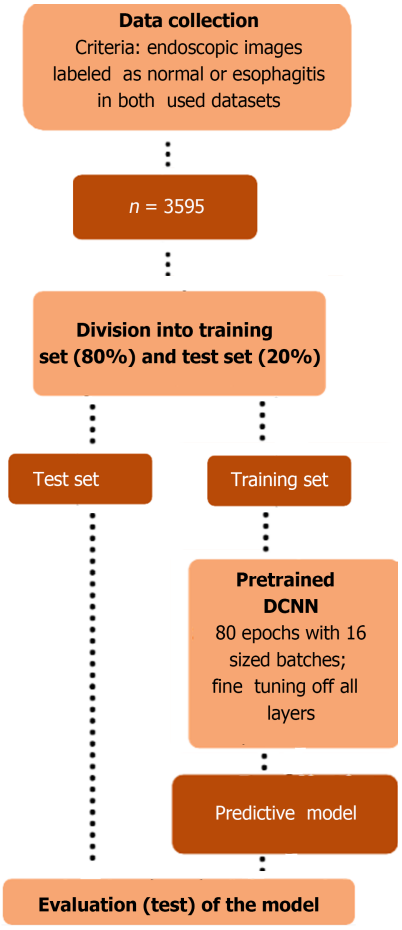

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Figure 2 Methodological design of the study. The proposed workflow encompasses selective collection of endoscopic images from the datasets, splitting and pre-processing of the data, iterative training of the classificatory model, and finally evaluation of its performance. DCNN: Dense convolutional neural network.

reasonable to assume that other esophageal lesions would be differentiated from the healthy aspect, and thus categorized together with the esophagitis images. Among the possible clinical differential situations, esophageal and esophagogastric junction cancers are of particular relevance. Upper endoscopies are considered by the Society of Thoracic Surgeons and the National Comprehensive Cancer Network as the initial diagnostic evaluation to exclude esophageal cancer[25]; although techniques such as chromoendoscopy and narrow band imaging are often used to increase the sensitivity of detection of lesions suggestive of malignancy, traditional endoscopic imaging still plays an important role in the investigational flowchart, and can demonstrate suspicious findings incidentally [26].

In view of this, in order to extend the clinical utility of our proposed algorithm to the investigation of potentially malignant endoscopic findings, two main approaches are possible: (1) Propose an adaptation of the model to multiclass classification and, to this end, retrain the model including endoscopic images of esophageal cancer, fine-tuning, if necessary, only the final layers, making appropriate changes in the final dense layer and in the loss function to accommodate 3 classes (thus, the final layer would now have 3 neurons with softmax activation function, and the sparse categorical crossentropy loss function would be adopted); and (2) Preserve the binary classification structure, but proposing to change the labels for normal and abnormal findings (thus, the model would be used to triage any endoscopic abnormalities, ranging from inflammatory findings to lesions suggestive of malignancy) and, for this purpose, retrain the model including endoscopic images representative of other types of lesions (including neoplastic lesions). In either situation, the incorporation of images representative of lesions suspicious for malignancy would be necessary, and the weights derived from training with normal endoscopic images and with esophagitis findings already performed would be used (same domain fine-tuning).

Convolutional neural networks with transfer learning for automated analysis of endoscopic images, as proposed in this study, may be incorporated into daily practice as a clinical decision support tool - screening abnormalities and indicating the need for further specialized evaluation or double checking medical reports. This application would add value especially in contexts of scarce resources, in which the number of endoscopists is limited and they are often poorly trained - increasing, thus, the likelihood

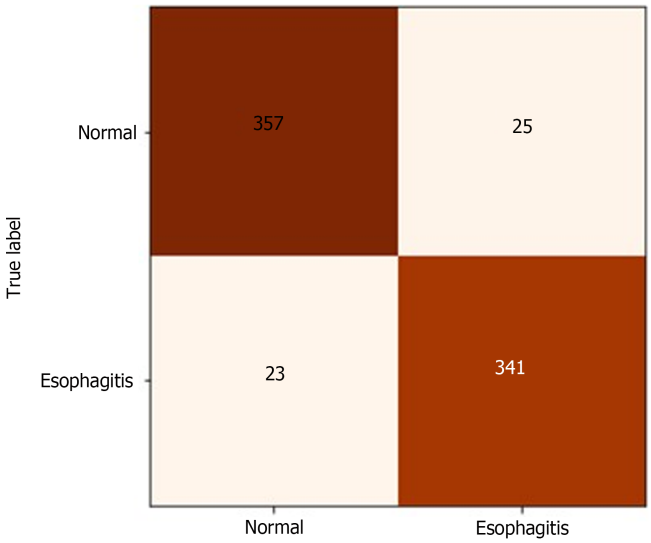

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Figure 3 Confusion matrix for the predictive model. As illustrated, the model was able to accurately classify 314 of 337 esophagitis images and 357 of 382 normal images, with true positive and false positive rates of 93.2% and 93.5%, respectively.

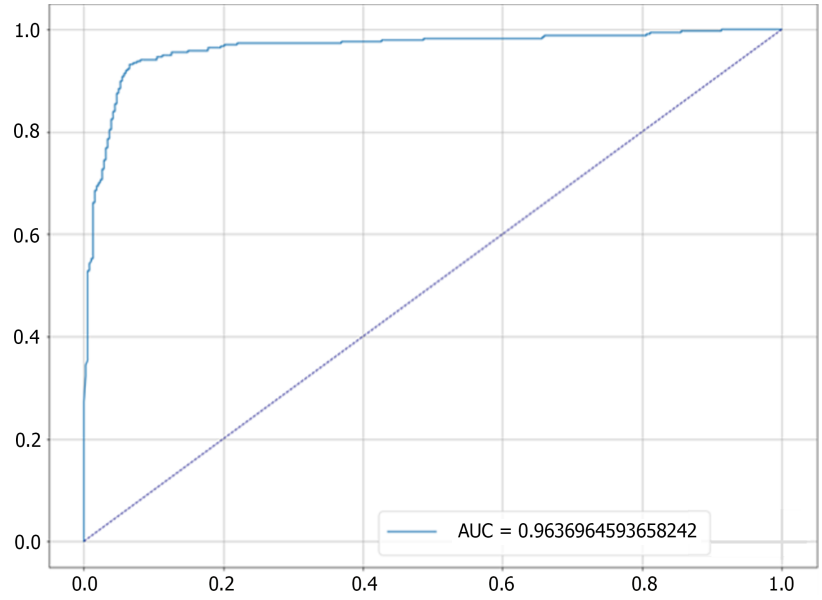

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Figure 4 Receiver operating characteristic curve for the proposed predictive model. The graph shows the resulting curve relating the true and false positive rates, giving an area on the curve of 96.4%. AUC: Area under the receiver operating characteristic curve.

of diagnostic errors. Moreover, it is especially promising as an adjunct tool to telemedicine, favoring rural and remote areas.

CONCLUSION

The use of deep learning, especially the transfer learning technique, has great potential field for the analysis of clinical images, including endoscopic records. Observing this great potential, this paper applied such technique, associated with retraining of all layers, to classify, with a 93.3% accuracy, esophageal mucosa images obtained from endoscopic studies according to the presence or absence of esophagitis. It then becomes evident the potential of transfer learning with fine-tuning for the analysis of images obtained by endoscopic method and recognition of esophageal lesions.

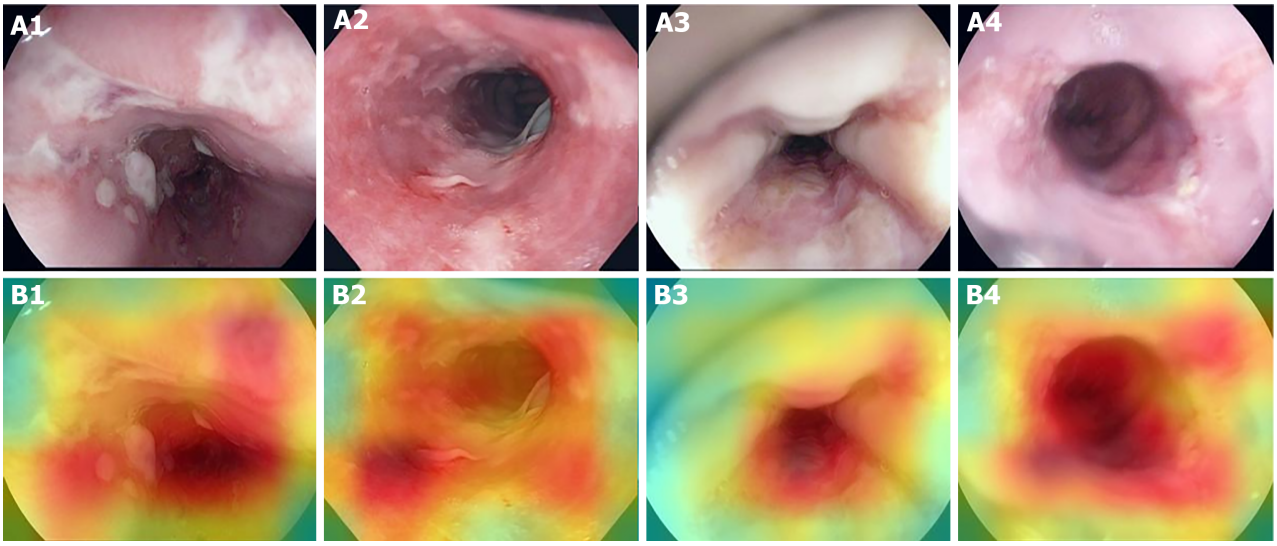

Figure 5 Heatmaps for spatial predictive relevance in esophagitis endoscopic images from test set. A and B: Images A1-A4 represent examples esophagitis endoscopic images used to test our predictive model, while images B1-B4 represent the corresponding heatmaps indicating, for each image, the areas with the greatest influence on the prediction. A1-A4: Citation: Pogorelov K, Randel K, Griwodz C, Eskeland S, Lange T, Johansen D, Spampinato C, Dang-Nguyen D, Lux M., Schmidt P, Riegler M, Halvorsen P. Kvasir: A Multi-Class Image Dataset for Computer Aided Gastrointestinal Disease Detection. MMSys'17 Proceedings of the 8th ACM on Multimedia Systems Conference (MMSYS); 2017 June 20-23; Taipei, Taiwan. New York: Association for Computing Machinery, 2017: 164-169. Copyright © Simula Research Laboratory 2017. Published by Association for Computing Machinery[12]. The authors have obtained the permission for figure using from the Simula Research Laboratory (Supplementary material). Citation: Borgli H, Thambawita V, Smedsrud PH, Hicks S, Jha D, Eskeland SL, Randel KR, Pogorelov K, Lux M, Nguyen DTD, Johansen D, Griwodz C, Stensland HK, Garcia-Ceja E, Schmidt PT, Hammer HL, Riegler MA, Halvorsen P, de Lange T. HyperKvasir, a comprehensive multi-class image and video dataset for gastrointestinal endoscopy. *Sci Data* 2020; 7: 283. Copyright © Simula Research Laboratory 2020. Published by Nature Publishing Group[13]. The authors have obtained the permission for figure using from the Simula Research Laboratory (Supplementary material).

In view of this, it is opportune to raise new studies involving transfer learning for the analysis of related data, with the aim of improving, disseminating and validating its use for the daily routine of clinical practice. Furthermore, the composition and dissemination high-quality endoscopic image sets representative of various clinical conditions (especially esophageal cancer, given its high clinical and epidemiological relevance) is essential for new studies to be developed and algorithms already proposed to be improved.

ARTICLE HIGHLIGHTS

Research background

Computer vision allied with deep learning, especially through the use of deep convolutional neural networks, has been increasingly employed in the automation of medical image analysis. Among these are endoscopic images, which are of great importance in the evaluation of a number of gastroenterological diseases.

Research motivation

Endoscopic findings constitute the diagnostic definition for esophagitis, a multietiological condition with significant impacts on quality of life and the possibility of evolution to a series of complications. Automating the identification of findings suggestive of esophageal inflammation using artificial intelligence could add great value to the evaluation and management of this clinical condition.

Research objectives

To identify whether a densely connected convolutional neural network with pre-trained and fine-tuned weights is able to binary classify esophageal Z-line endoscopic images according to the presence or absence of esophagitis.

Research methods

Endoscopic images of 1932 patients with a diagnosis of esophagitis and 1663 patients were splitted in training (80%) and test (20%) and used to develop and evaluate a binary deep learning classifier built using a pre-trained DenseNet-201 architecture. The classifier model performance was evaluated in the test set according to accuracy, sensitivity, specificity and area under the receiver operating characteristic

curve.

Research results

The proposed model was able to diagnose esophagitis in the validation set with sensitivity of 93.18 and specificity of 93.46, demonstrating the feasibility of using deep transfer learning to discriminate normal from damaged mucosa in endoscopic images of the same anatomical segment. It remains to be investigated whether, by means of a more diverse set of images, this technique can be proposed to identify different types of esophageal abnormalities, and potentially in other organs.

Research conclusions

Convolutional neural networks with transfer learning for automated analysis of endoscopic images, as proposed in this study, demonstrate potential for incorporation into clinical practice as a clinical decision support tool, mainly benefiting scarce resources settings.

Research perspectives

Sets of endoscopic images representative of various clinical conditions should be published, in order to allow the findings of this study to be externally validated and for new models with different classificatory approaches to emerge.

FOOTNOTES

Author contributions: Caires Silveira E proceeded the data collection/entry, performed data analysis and data interpretation, developed the proposed predictive model and participated in preparation and review of manuscript; Santos Corrêa CF and Madureira Silva L participated in preparation of manuscript and wrote the literature analysis/search; Mattos Pretti S and Almeida Santos B participated in review of manuscript; Freire de Melo F designed the research and participated in review of manuscript.

Institutional review board statement: For this study, there was no need for an appraisal by an ethics committee, since only publicly available anonymized data were used.

Informed consent statement: The present manuscript used anonymous images to produce its analyzes and results, in a method that obeys the norms of medical bioethics. Thus, there was no direct or even indirect contact between researchers and patients, with no necessity for "Signed Informed Consent Form" to carry out our study.

Conflict-of-interest statement: The authors have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Why is endosonography insufficient for residual diagnosis after neoadjuvant therapy for esophageal cancer? Solutions using muscle layer evaluation

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Abstract

BACKGROUND

The diagnosis of residual tumors using endoscopic ultrasound (EUS) after neoadjuvant therapy for esophageal cancer is considered challenging. However, the reasons for this difficulty are not well understood.

AIM

To investigate the ultrasound imaging features of residual tumors and identify the limitations and potential of EUS.

METHODS

This exploratory prospective observational study enrolled 23 esophageal squamous cell carcinoma patients receiving esophagectomy after neoadjuvant therapy [15 patients after neoadjuvant chemotherapy (NAC) and 8 patients after chemoradiotherapy (CRT)] at the Department of Surgery, Chiba University Hospital, between May 2020 and October 2021. We diagnosed the T stage for specimens using ultrasound just after surgery and compared ultrasound images with the cut surface of the fixed specimens of the same level of residual tumor. The ratio of esophageal muscle layer defect measured by ultrasound was compared with clinicopathological factors. Furthermore, the rate of reduction for the muscle layer defect was evaluated using EUS images obtained before and after neoadjuvant therapy.

RESULTS

The accuracy of T stage rate was 61% (n = 14/23), which worsened after CRT

(38%, n = 3/8) than after NAC (73%, n = 11/15) because of overstaging. Moreover, pT0 could not be diagnosed in all cases. The detection rate of residual tumor for specimens using ultrasound retrospectively was 75% (n = 15/20). There was no correlation between after-NAC (79%, n = 11/14) and after-CRT (67%, n = 4/6) detection rate. The detection of superficial and submucosal types was poor. The pathologic tumor size and pathological response were correlated. Tumor borders were irregular and echogenicity was mixed type after CRT. There was a correlation between the pT stage (pT0/1 *vs* pT2/3) and the length of muscle layer circumference (P = 0.025), the length of muscle layer defect (P < 0.001), and the ratio of muscle layer defect (P < 0.001). There was also a correlation between the pT stage and the rate of muscle layer defect reduction measured by EUS (P = 0.001).

CONCLUSION

Compared to pathological images, some tumors are undetectable by ultrasound. Focusing on the esophageal muscle layer might help diagnose the depth of the residual tumor.

Key Words: Esophageal cancer; Esophageal squamous cell carcinoma; Neoadjuvant therapy; Endoscopic ultrasound; Residual tumor; Endosonography

Core Tip: This exploratory prospective observational study evaluated the effectiveness of endoscopic ultrasound (EUS) in diagnosing residual tumors after neoadjuvant therapy for esophageal squamous cell carcinoma. It is well known that the diagnosis using EUS after neoadjuvant therapy is inaccurate. The results of ultrasound for surgical specimens are not satisfactory as well. Our study found that the inability to distinguish scar tissue from the tumor made detection and diagnosis impossible in some residual tumors. Esophageal muscle layer defect as an indirect finding correlated with the depth of the residual tumor. These insights could help improve the diagnosis of residual tumors.

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INTRODUCTION

Esophageal cancer is the seventh most common cancer worldwide in terms of incidence and the sixth most common in terms of mortality. Especially in Asia, esophageal squamous cell carcinoma (ESCC) accounts for more than 90% of all esophageal cancers[1]. There is strong evidence supporting the superiority of neoadjuvant chemoradiotherapy (CRT) and neoadjuvant chemotherapy (NAC) plus surgery over surgery alone for locally advanced esophageal cancer[2]. In ESCC patients, pathological complete response (pCR) was 62% after CRT and 2%-7% after NAC[3-5]. While patients with pCR may have avoided unnecessary esophagectomy, the residual tumor must be accurately identified to justify not performing a surgical resection.

In contrast, residual tumors after CRT and NAC are often present only at a depth of the esophageal wall, without any exposure to the superficial mucosa[6,7]. Although Endoscopic ultrasound (EUS) has a well-established role in the initial staging of esophageal cancer[8], the diagnosis of esophageal cancer after neoadjuvant therapy has been controversial. EUS sensitivity for residual tumors at the primary site after neoadjuvant CRT is as high as 0.96; however, the specificity is as low as 0.08, and thus it does not seem to be sufficiently accurate to detect residual tumor[9]. In addition, the accuracy of staging after NAC is not sufficient[10]. Several studies have correlated EUS measurements with tumor regression grade and survival. However, it is unclear whether the echogenic lesions detected using EUS are indeed residual tumors and how they appear on ultrasound. The purpose of this study was to characterize the ultrasound images of residual tumors, explore the limitations of EUS, and assess its potential in residual diagnosis.

MATERIALS AND METHODS

Patient population

This exploratory prospective observational study was conducted in two steps. The first step (study 1) aimed to investigate the limitations and characteristics of residual tumor diagnosis using ultrasound. Based on study 1, the second step (study 2) aimed to implement EUS to detect remanent tumors deep in the muscle layer. Study 1 enrolled 23 ESCC patients undergoing esophagectomy after neoadjuvant therapy, including NAC or CRT in the Department of Surgery, Chiba University Hospital, between May 2020 and October 2021. All patients were histologically proven to have ESCC based on biopsy specimens. The clinical stage was determined by endoscopy, barium esophagography, chest and abdominal computed tomography (CT) scans, and 18F-fluorodeoxyglucose positron emission tomography, based on the 11th Edition of the Japanese Classification of Esophageal Cancer[11]. Study 2 enrolled 20 out of the initial 23 participants in the first study who underwent EUS for staging and were diagnosed with cT2 or deeper. Our Institutional Review Board (IRB No. 3550) approved this study. We obtained written informed consent from patients for all examinations and treatments.

Preoperative and surgical treatment

As recommended by the Japanese Clinical Oncology Group (JCOG) 9907 Study, we performed preoperative chemotherapy postoperatively for patients with clinically UICC stage II/III resectable ESCC in our department's criteria[5]. NAC was composed of two cycles of 5-fluorouracil (800 mg/m^2 infusion for five consecutive days) and cisplatin (80 mg/m^2 on day 1). Some patients received three cycles of docetaxel (70 mg/m^2 on day 1), cisplatin (70 mg/m^2 on day 1) and 5-fluorouracil (750 mg/m^2 infusion for five consecutive days) based on the JCOG 1109 study[12]. After NAC, all patients were evaluated by CT, PET, and endoscopy, and underwent radical esophagectomy with three-field lymphadenectomy, including cervical, mediastinal, and abdominal lymph node dissection. CRT was composed of 2 Gy/fraction at a total dose of 40 Gy with a long-T radiation field from the cricoid cartilage to the upper abdomen, including the gross tumor volume. Concurrent chemotherapy was performed with 5-fluorouracil (500 mg/m^2 infusion on day 0-4) and cisplatin (15 mg/m^2 on day 1-5). After receiving a 40 Gy dose, all patients were evaluated by CT, PET, and endoscopy. An additional 20 Gy dose was delivered to patients with potentially resectable tumors, making the total irradiation dose 60 Gy (definitive CRT), and concurrent chemotherapy with the same regimen was also provided. After CRT, patients with resectable tumors underwent radical esophagectomy with three-field lymphadenectomy four weeks after CRT. The criteria for the pathological response of primary tumor were categorized as ineffective (Grade 0); viable cancer cells accounted for 1/3 or more of tumor tissue (Grade 1); viable cancer cells accounted for less than 1/3 of tumor tissue (Grade 2); no viable cancer cells (Grade 3).

Procedure of ultrasound for surgical specimens

In study 1, the surgical specimens of all patients were collected from the operation room, and an ultrasound was performed immediately. The unfixed specimens immersed in saline solution were scanned vertically and horizontally using 15 MHz electronic linear ultrasound. The imaging procedure was recorded on video. We used LOGIQ S8 (GE Healthcare Japan Corporation, Tokyo, Japan) ultrasound platform in all studies. The ultrasound for specimens showed the mucosal layer, submucosal layer, inner muscle layer, intermuscular connective tissue layer, and outer muscle layer, as shown in EUS. We diagnosed the presence and depth of the tumor on the day of surgery before pathology results were known. We assessed the accuracy of diagnosing residual tumor depth using ultrasound. The prefix "u" indicates ultrasound diagnosis. Furthermore, to clarify the characteristic features of residual tumor, we compared ultrasound images with the cut surface of the fixed specimens at the same level of tumor site in the esophageal wall.

Measurements of muscle layer defect

In study 1, in addition to the direct finding of the tumor, we focused on the esophageal muscle layer as an indirect finding, which is the most visible on ultrasound. We set up a cross-sectional image vertical to the esophagus at the center of the tumor. We measured the length of muscle layer circumference and the length of muscle layer defect. We calculated the ratio of muscle layer defect and compared each pathological factor.

Muscle layer defect angle

Study 2 aimed to evaluate the muscle layer defect using EUS. However, the EUS and ultrasound findings for specimens were different since the specimens were fully stretched. Keeping the esophageal wall stretched *in vivo* and measuring the circumference of the muscle layer by EUS would be challenging. Therefore we substituted the ratio of muscle layer defect with the total circumference of the muscle layer by the angle and named it as muscle layer defect angle (MDA). MDA was defined as the angle between the center of the lumen and the two points where EUS could not help visualize the inner muscle and intermuscular connective tissue layer. Using MDA, we measured the percentage of

improvement in muscle layer defect caused by neoadjuvant therapy using the still images as well as video images of EUS. EUS was performed before and after neoadjuvant therapy by three or more skilled endoscopists. We calculated the MDA reduction rate using Pre-MDA and Post-MDA. MDA reduction rate was expressed using the following equation:

MDA reduction rate (%) = {[PreMDA(°) - PostMDA(°)] / PreMDA(°)} × 100

We compared each MDA factor with the pathological T stage. The echo images were analyzed using ImageJ software (National Institutes of Health, available at http://rsb.info.nih.gov/ij) specialized for morphological evaluation.

Statistical analysis

This study compared the results of prospectively collected data after confirming pathology. All statistical analyses were conducted with the JMP® Pro software program, version 13.2 (SAS Institute Inc., Cary, NC, United States). Continuous variables were expressed as median (min–max) or mean (± SD). Fisher's exact test was used to compare and analyze categorical variables. Continuous variables were analyzed using Wilcoxon's signed-rank sum test. P values of < 0.05 were considered statistically significant. Receiver operating characteristics (ROC) analysis was performed to assess the highest diagnostic values to determine the optimal cut-off points.

RESULTS

Patients' characteristics

From May 2020 to October 2021, 61 patients underwent esophagectomy for esophageal cancer, and 37 patients underwent neoadjuvant therapy in our department. Of these, we excluded 5 patients with adenocarcinoma, 2 patients with neuroendocrine carcinoma, and 7 patients whose surgical specimens could not be analyzed using ultrasound. The clinical characteristics and pathological examination are summarized in Table 1. Fifteen patients received NAC, of which 13 patients received cisplatin plus 5-fluorouracil (CF), and 2 patients received docetaxel plus cisplatin plus 5-fluorouracil (DCF). Eight patients received CRT, of which 6 patients received 38-40 Gy irradiation, and 2 patients received additional irradiation to the total of 60 Gy as their tumors were considered unresectable by the end of 40 Gy irradiation. These two patients underwent salvage surgery after the additional irradiation. Three patients achieved pathological pCR (pathological grade 3); of these, 2 patients received CRT, and 1 patient received NAC only.

The diagnosis of uT stage with ultrasound for specimens

We diagnosed uT stage by ultrasound for specimens just after surgery (Table 2). There was poor agreement between uT and pT stages. The overall accuracy uT stage rate was 61% (n = 14/23). The respective accuracy uT stage rate was 0% (n = 0/3) for pT0, 0% (n = 0/3) for pT1a, 67% (n = 4/6) for pT1b, 67% (n = 2/3) for pT2, and 100% (n = 8/8) for pT3. All pT0 and pT1a patients could not be diagnosed. Regarding comparison with NAC and CRT, the overall accuracy of uT stage rates were 73% (n = 11/15) and 38% (n = 3/8), respectively. The overall accuracy of overstaging uT stage rates was 13% (n = 2/15) and 62% (n = 5/8), respectively.

Detect for residual tumor retrospectively

Among 20 patients, excluding 3 patients who achieved complete response, we compared ultrasound images with the cut surface of the fixed specimens of the same level of residual tumor site in the esophageal wall to examine whether the residual tumor itself could be detected (Table 3). The overall detection rate for residual tumors was 75% (n = 15/20), with no correlation between after NAC (79%, n = 11/14) and after CRT (67%, n = 4/6). The macroscopic types after neoadjuvant therapy were classified into two groups; 11 patients had ulcerative and protruding tumor types, while 9 patients had superficial and submucosal tumors. The superficial and submucosal types were poorly detected (P = 0.008). In addition, pathologic tumor size and the pathological response showed a significant correlation (P = 0.008, 0.127). Echoic characteristics of the residual tumor are shown in Table 4.

The tumor borders were relatively regular, and echogenicity was hypoechoic after NAC. In contrast, tumor borders were irregular, and echogenicity was hypo and iso (mixed) echoic type in all patients after CRT (Figure 1).

Relationship between muscle layer measurements and pathological characteristics

We measured the muscle layer using ultrasound images (Figure 2). Ultrasound showed a clearly defined disruption of the muscle layer. We compared muscle layer factors with pathological characteristics (Figure 3). There was a significant correlation between pT stage (pT0/1, n = 12 *vs* pT2/3, n = 11) and length of muscle layer circumference (36.2 ± 5.9 mm *vs* 44.3 ± 8.9 mm, P = 0.025), length of muscle layer defect (22.5 ± 8.0 mm *vs* 7.1 ± 7.2 mm, P < 0.001), and the ratio of muscle layer defect (63.0 ± 22.8% *vs* 16.1 ± 16.0%, P < 0.001).

Table 1 Patients' characteristics

	All population (*n* = 23)	NAC (*n* = 15)	CRT (*n* = 8)
Age (yr)			
Median (range)	72 (43-81)	72 (43-78)	72 (49-81)
Sex			
Male	19	12	7
Female	4	3	1
Tumor location			
Ut	2	2	0
Mt	15	8	7
Lt	4	4	0
Ae	2	1	1
Clinical T stage			
cT1b	1	1	0
cT2	3	3	0
cT3	11	11	0
cT4a	1	0	1
cT4b	7	0	7
Chemotherapy regimen			
CF	21	13	8
DCF	2	2	
Total irradiation dose			
38-40Gy	6		6
60Gy	2		2
Time of surgery after therapy (d)			
Median (range)	37 (31-61)	36 (31-61)	40 (35-57)
Pathological T stage			
pT0	3	1	2
pT1a	3	1	2
pT1b	6	6	0
pT2	3	1	2
pT3	8	6	2
Pathological response			
Grade1	13	11	2
Grade2	7	3	4
Grade3	3	1	2

Ut: Upper thoracic esophagus; Mt: Middle thoracic esophagus; Lt: Lower thoracic esophagus; Ae: Abdominal esophagus; CF: Cisplatin plus 5-fluorouracil; DCF: Docetaxel plus cisplatin plus 5-fluorouracil; NAC: Neoadjuvant chemotherapy; CRT: Chemoradiotherapy.

There was no correlation between pathological response (Grade 1/2, n = 20 *vs* Grade 3, n = 3) and length of muscle layer circumference (40.0 ± 9.0 mm *vs* 42.6 ± 4.9 mm, P = 0.438), length of muscle layer defect (14.5 ± 11.5 mm *vs* 14.6 ± 4.5 mm, P = 1.00), and the ratio of muscle layer defect (39.2 ± 32.9% *vs* 33.8 ± 6.8%, P = 0.927).

Table 2 Comparison Ultrasound for specimens uT stage to histological pT stage

Ultrasound T stages	pT0	pT1a	pT1b	pT2	pT3	Total
	Pathological T stages after NAC and CRT					
uT0	0	1	1	0	0	2
uT1a	0	0	0	0	0	0
uT1b	0	0	4	0	0	4
uT2	1	1	1	2	0	5
uT3	2	1	0	1	8	12
Total	3	3	6	3	8	23
Accuracy (%)	0	0	67	67	100	61
Overstaging (%)	100	67	17	33	0	30
Understaging (%)		33	16	0	0	9
	Pathological T stages after NAC					
uT0	0	1	1	0	0	2
uT1a	0	0	0	0	0	0
uT1b	0	0	4	0	0	4
uT2	1	0	1	1	0	3
uT3	0	0	0	0	6	6
Total	1	1	6	1	6	15
Accuracy (%)	0	0	67	100	100	73
Overstaging (%)	100	0	17	0	0	13
Understaging (%)		100	17	0	0	13
	Pathological T stages after CRT					
uT0	0	0	0	0	0	0
uT1a	0	0	0	0	0	0
uT1b	0	0	0	0	0	0
uT2	0	1	0	1	0	2
uT3	2	1	0	1	2	6
Total	2	2	0	2	2	8
Accuracy (%)	0	0	0	50	100	38
Overstaging (%)	100	100	0	50	0	62
Understaging (%)		0	0	0	0	0

NAC: Neoadjuvant chemotherapy; CRT: Chemoradiotherapy.

Relationship between MDA and pathological T stage

In study 2, we measured MDA using EUS images (Figure 4). To confirm the reduction of muscle layer defect after adjuvant therapy compared to before, we excluded 3 patients (EUS before therapy did not show muscle layer invasion in 2 patients, and 1 patient did not undergo EUS before therapy). The clinical characteristics and pathological examination results are summarized in Table 5. There was no significant difference between pT0/1 and pT2/3 in terms of clinical characteristics. MDA factors were compared with pathological T stage (Figure 5). There was no correlation between preoperative treatment (NAC, n = 12 *vs* CRT, n = 8), pre-MDA (50.0 ± 35.3° *vs* 70.0 ± 27.9°, P = 0.137), post-MDA (30.5 ± 33.6° *vs* 43.2 ± 28.4°, P = 0.279), and MDA reduction rate (51.4 ± 34.9% *vs* 40.4 ± 25.7%, P = 0.589). There was a significant correlation between pT stage (pT0/1, n = 10 *vs* pT2/3, n = 10), pre-MDA (142.5 ± 110.6° *vs* 274.0 ± 91.7°, P = 0.039), post-MDA (45.9 ± 49.3° *vs* 210.0 ± 98.7°, P < 0.001), and MDA reduction rate (68.9 ± 24.4% *vs* 25.1 ± 20.3%, P = 0.001).

Table 3 Relationship between detection of residual tumor and clinicopathological factors

	Detection of residual tumor		
	Possible	Impossible	*P*
All, *n* (%)	15 (75)	5 (25)	
Preoperative treatment, *n* (%)			
NAC	11 (79)	3 (21)	
CRT	4 (67)	2 (33)	0.613
Macroscopic type after neoadjuvant therapy, *n* (%)			
Ulcerative and protruding type	11 (100)	0 (0)	
Superficial and SMT type	4 (44)	5 (56)	0.008
Pathologic tumor size (mm)			
Median (range)	42 (5-65)	4 (2-34)	0.008
Pathological T stage, *n* (%)			
pT1a/1b	5 (56)	4 (44)	
pT2/3	10 (91)	1 (9)	0.127
Pathological response, *n* (%)			
Grade1	12 (92)	1 (8)	
Grade2	3 (43)	4 (57)	0.031

NAC: Neoadjuvant chemotherapy; CRT: Chemoradiotherapy.

Table 4 Echoic characteristics of the detected residual tumor

	All population (*n* = 15)	NAC (*n* = 11)	CRT (*n* = 4)	*P*
Border				
Regular	10	10	0	
Irregular	5	1	4	0.004
Echogenicity				
Hypoechoic	5	5	0	
Hypo and isoechoic (mixed)	10	6	4	0.231

NAC: Neoadjuvant chemotherapy; CRT: Chemoradiotherapy.

We conducted ROC analysis to determine the optimal MDA reduction rate cut-off points that could yield the maximum difference between the two groups (Figure 6). From this ROC curve analysis, 57.0% was determined as the best cut-off rate to detect the patients in the pT0/1 group with the highest accuracy. Based on the optimal cut-off values of the MDA reduction rate, that could distinguish the pT0/1 group with a sensitivity of 0.80, specificity of 0.90, and accuracy of 0.93.

DISCUSSION

We conducted two studies; study 1 was performed to investigate the limitations and characteristics of residual tumor diagnosis using ultrasound and study 2 aimed to implement EUS to detect remanent tumors deep in the muscle layer. The first study revealed the limitations and potential of ultrasound for residual tumors. After cross-referencing ultrasound images with the correct pathological diagnosis, some residual tumors were found to be undetectable on ultrasound. In contrast, the ratio of the esophageal muscle layer defect, which was not focused upon so far, was considered helpful in diagnosing the depth of the residual tumor. In the second study, muscle layer defect was measured using EUS. The results showed that the rate of muscle layer defect reduction in neoadjuvant therapy

Table 5 Patients' characteristics in study 2

	pT0/1 (*n* = 10)	pT2/3 (*n* = 10)	*P*
Age (yr)			
Median (range)	73 (52-79)	72 (43-81)	0.94
Sex			
Male/Female	9/1	7/3	0.582
Tumor location			
Ut, Mt, Lt/Ae	10/0	8/2	0.473
Clinical T stage			
cT2, 3/cT4a, b	6/4	6/4	1
Preoperative treatment			
NAC/CRT	6/4	6/4	1
Chemo regimen			
CF/DCF	9/1	9/1	1
Total irradiation dose			
38-40Gy/60Gy	2/2	4/0	0.429
Time of EUS after therapy (d)			
Median (range)	37 (21-49)	29 (14-50)	0.172
Time of surgery after therapy (d)			
Median (range)	41 (34-57)	37 (31-61)	0.471

Ut: Upper thoracic esophagus; Mt: Middle thoracic esophagus; Lt: Lower thoracic esophagus; Ae: Abdominal esophagus; CF: Cisplatin plus 5-fluorouracil; DCF: Docetaxel plus cisplatin plus 5-fluorouracil; NAC: Neoadjuvant chemotherapy; CRT: Chemoradiotherapy.

correlated with the pathological depth of the tumor. Our findings can help improve EUS diagnosis and provide more treatment options for ESCC patients after neoadjuvant therapy.

We considered comparing pathological and ultrasound images. However, using only EUS was considered unreliable for the following reasons. First, it was difficult to compare the measured level of tumor site in the esophagus with the level of the fixed specimens. Second, EUS was good for evaluating targeted areas but not for scanning large areas. In contrast, ultrasound for surgical specimens allowed us to compare pathological and ultrasound images with the same level of ultrasound images and scans of the entire lesion. This could help clarify whether the modality of echo itself contributes to the residual diagnosis after neoadjuvant therapy.

According to several meta-analyses examining the accuracy of detecting residual tumors for esophageal cancer after CRT, the consensus was that EUS had high sensitivity but low specificity[10,13]. Even after NAC, the concordance rate between EUS and pathological T-stage was reportedly as low as 29%, and the depth was overstaged in more than half of the cases (51%)[14]. It is well known that tumor invasion might be overestimated due to inflammation within and surrounding the tumor[15]. Our study showed 61% accuracy and 30% overstaging of uT, which was better than previous studies. Even though the ultrasound on surgical specimens was performed in a stable environment, these results are not sufficiently accurate. A previous study analyzing the accuracy of EUS in patients with esophageal cancer after NAC or CRT showed that accuracy of uT was significantly worse after CRT (16%) than after NAC (43%)[16]. In line with this previous study, our results showed that the accuracy of uT worsened after CRT (38%) than after NAC (73%). Our study showed that CRT downstaged tumors more effectively than NAC. As a result, there were more tumors with pT0 and pT1a, which were difficult to detect using ultrasound. All pT0 and pT1a patients could not be diagnosed because the scar tissue associated with tumor disappearance was misidentified as a residual tumor, causing overstaging. Diagnosing T3 was easy because the esophageal muscle layer was destroyed or replaced by fibrosis. However, distinguishing between a residual tumor and a fibrosis tissue seemed impossible.

We also examined the retrospective detection rate for residual tumor and the echoic characteristics of the residual tumor by comparing ultrasound images with the cut surface of the fixed specimens of the same level of the esophageal wall. Our results showed no difference in the detection rate after CRT and after NAC; however, the after CRT specimens appeared to have an irregular border and mixed echogenicity. According to a study that classified the echogenicity of gastrointestinal tumors, most

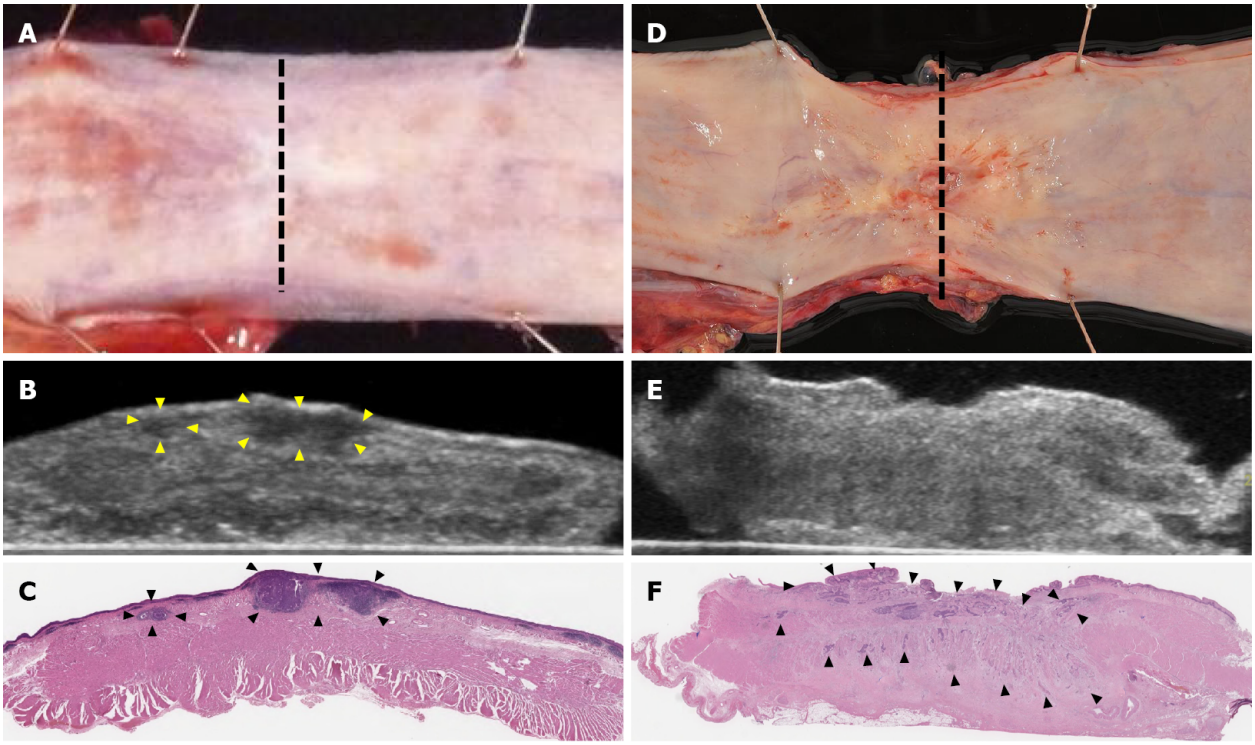

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Figure 1 Ultrasound for specimens. A: In the after neoadjuvant chemotherapy cases, the residual tumor was SMT type with no exposure to the mucosal surface; B: Ultrasound showed the tumor as hypoechoic with regular borders (arrowhead); C: Pathology showed 18 mm × 18 mm, pT1b-SM3 (arrowhead). The pathological response was Grade1; D: After chemoradiotherapy, the residual tumor was ulcerative type; E: Ultrasound showed the tumor as mixed echoic with irregular borders; F: Pathology showed 45 mm × 20 mm, pT3 (arrowhead). The pathological response was Grade1.

esophageal cancers expressed echo levels between the muscularis propria and the deep mucosa[17]. However, our study showed that the residual tumors lost heterogeneity and higher echogenicity after CRT compared to deep mucosa. This result indicated that the preoperative treatment increased the brightness of echogenicity. In a previous pathological study, chemotherapy was found to generally decrease tumor cellularity and cause fragmentation of cell nuclei. Additionally, in squamous cell carcinoma, chemotherapy is known to increase keratinization with the formation of keratin pearls, acellular keratin with islands of nonviable tumor cells, histiocytic giant cells, and lymphocytes surrounding tumor cells in squamous cell carcinoma[18]. Our pathological findings after neoadjuvant therapy, particularly after CRT, showed that the density of collagen fibers increased as the cancer cells disappeared. Consequently, the ratio of cancer cells to stromal components also changed, which might have led to a difference in echo level, such as mixed echogenicity. The increase in the echogenicity of tumors is reportedly related to the positive response to NAC in breast tumors[19]. Although such phenomena correlating echogenicity and treatment effect are not reported for esophageal cancers, and our study could not prove the relationship, some changes in echogenicity of ESCC could be attributed to treatment.

When predicting patient prognosis after CRT or NAC, it is reasonable to measure the reduction in tumor volume using EUS. However, the conventional measurement method involving direct identification and measurement of the tumor is not accurate. Several studies have assessed the predictive value of tumor thickness and area using EUS to determine patient prognosis and tumor regression in patients with esophageal cancer undergoing NAC or CRT[20-23]. Although these studies focused on lesions identified on EUS, our results showed that EUS could not detect the residual tumor. Tumors were either scattered on the esophageal wall, had unclear borders, or were scar tissue that appeared like a tumor.

For this reason, we considered it inappropriate to include EUS-confirmed echo lesions as residual tumors. In our clinical experience, we have observed that the esophageal muscle layer can be clearly visualized using EUS in patients with a good response to neoadjuvant therapy. Therefore, we focused on the esophageal muscle layer as indirect findings instead of the tumor. In the first study, ultrasound findings for specimens in the group with pT0 and pT1 showed that the muscle layer circumference was longer, the length of muscle layer defect was shorter, and the rate of muscle layer defect was lower than in the group with pT2 and pT3. Tissue heterogeneity was noted if residual cancer cells remained in the muscle layer or deeper; in such cases, we could not explore the muscle layer using ultrasound findings. In addition, it was improbable that the muscle layer destroyed by tumor invasion could be regenerated,

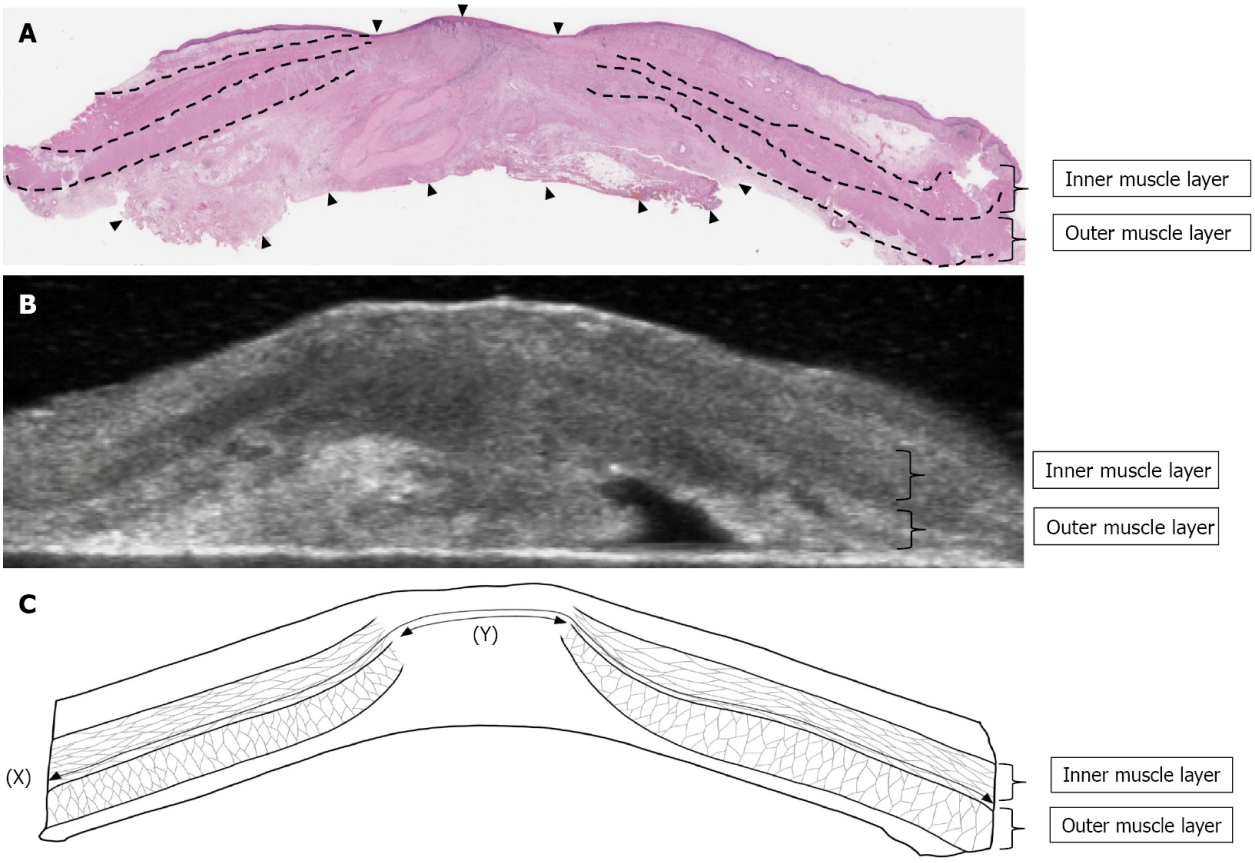

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Figure 2 Measurements of muscle layer defect. A: In this case of cT4b to pT1a after chemoradiotherapy, most of the primary tumors were replaced by degenerative tissue (arrowhead), and the muscle layer was taking over; B: Ultrasound for specimens showed a clearly defined disruption of the muscle layer; C: Length of muscle layer circumference (X) was 45 mm. The length of the muscle layer defect (Y) was 12 mm. In this case, the ratio of muscle layer defect was 27%.

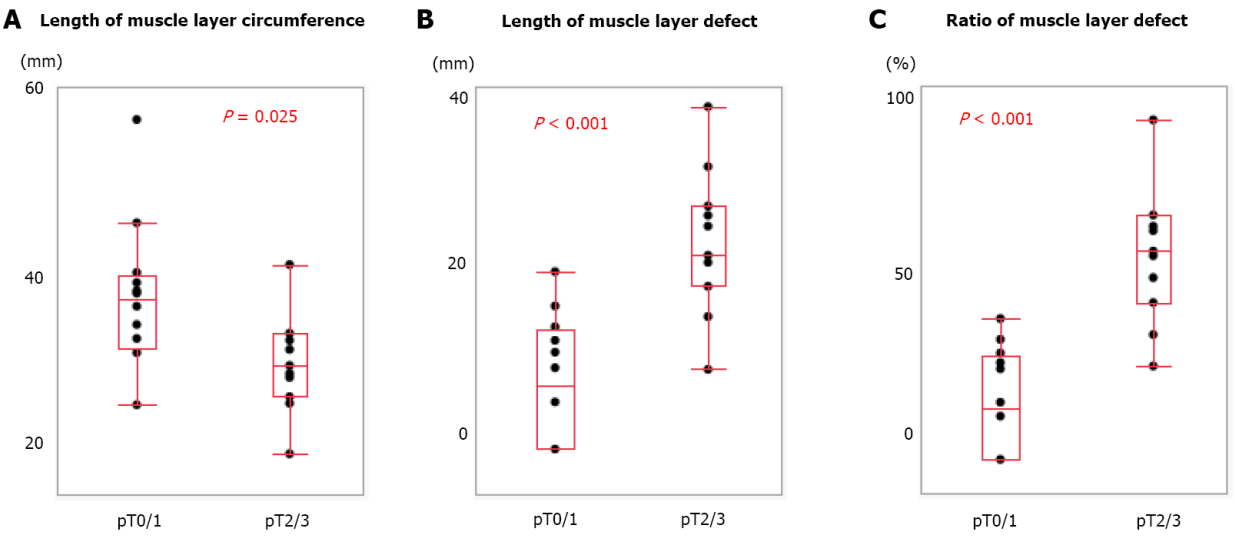

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Figure 3 Relationship between muscle layer measurements and pathological characteristics. A: Length of muscle layer circumference correlated with pT (pT0/1 *vs* pT2/3); B: Length of muscle layer defect correlated with pT; C: Ratio of muscle layer defect correlated with pT.

at least during the observation period. We considered that the reduction in the muscle layer defect in the specimens with stages pT0 and pT1 was because of scar contraction caused by the disappearance of the tumor due to neoadjuvant therapy. In the second study, findings of EUS performed before and after neoadjuvant therapy in the group with pT0 and pT1 showed that pre-MDA was smaller, post-MDA was smaller, and MDA reduction rate was larger in the groups with pT2 and pT3 staging. The improvement

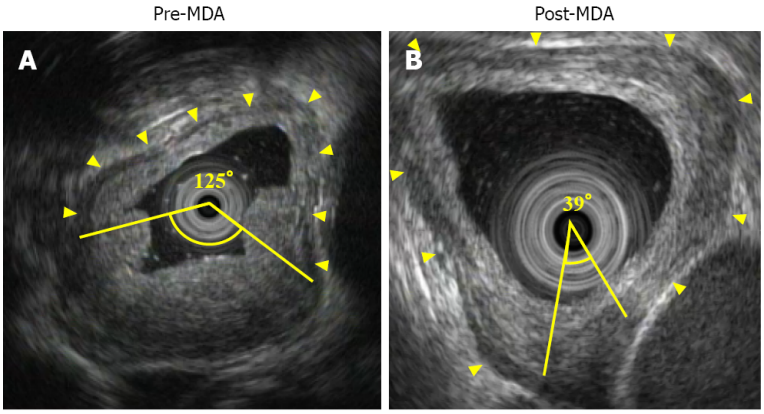

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Figure 4 Measurements of muscle layer defect angle. A: Endoscopic ultrasound showed the normal muscle layer as hypoechoic inner muscle layer, hyperechoic intermuscular connective tissue layer, and hypoechoic outer muscle layer (arrowhead). In this case of cT3 before neoadjuvant chemotherapy (NAC), pre-muscle layer defect angle (MDA) was 125°; B: After NAC, post-MDA was 39°, and thus MDA reduction rate was 34.8%. This case achieved pCR.

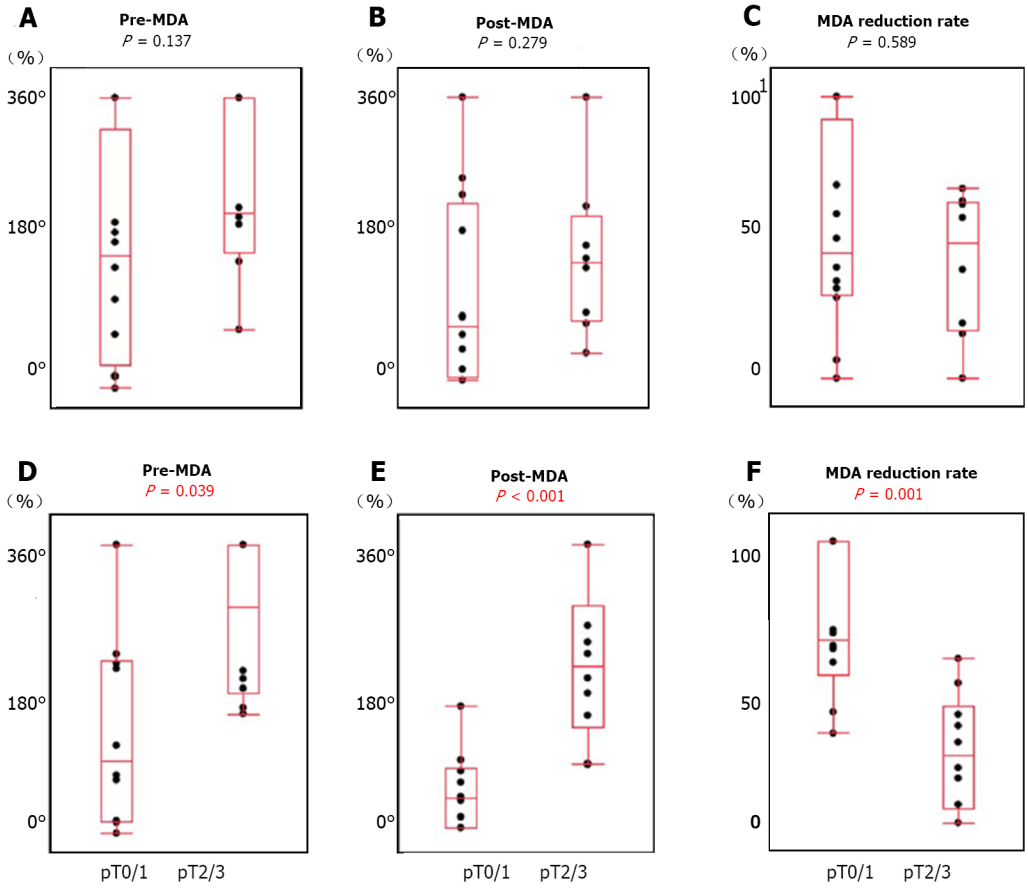

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Figure 5 Relationship between muscle layer defect angle measurements and clinicopathological factors. A: Pre-muscle layer defect angle (MDA) not correlated with preoperative treatment [neoadjuvant chemotherapy (NAC) *vs* chemoradiotherapy (CRT)]; B: Post-MDA not correlated with preoperative treatment (NAC *vs* CRT); C: MDA reduction rate not correlated with preoperative treatment (NAC *vs* CRT); D: Pre-MDA correlated with pT (pT0/1 *vs* pT2/3); E: Post-MDA correlated with pT (pT0/1 *vs* pT2/3); F: MDA reduction rate correlated with pT (pT0/1 *vs* pT2/3).

of the muscle layer defect was considered useful in EUS depth diagnosis.

If EUS helps diagnose pCR or superficial residual tumors and deep remanent tumors in patients after neoadjuvant therapy by focusing on the muscle layer, the clinical treatment options can be expanded significantly. In recent years, endoscopic salvage resection has been preferred over esophagectomy for patients with superficial localized residual tumors after CRT[24,25]. In addition, it was reported that overall, 29% of patients with esophageal cancer achieved pCR after neoadjuvant CRT[26], and 62% of

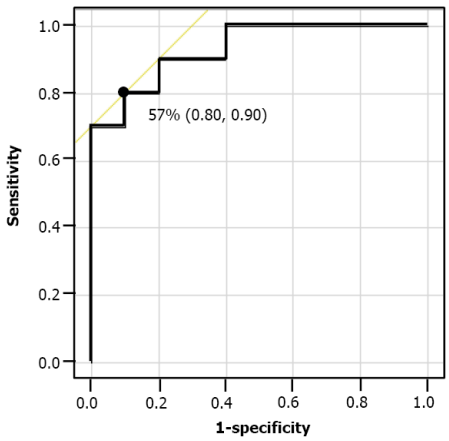

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Figure 6 Receiver operating characteristics curve of the muscle layer defect angle reduction rate. The AUS was 0.93, and 57% was the optimal cut-off value to detect the patients in the pT0/1 group with the highest accuracy.

patients with ESCC achieved pCR according to the JCOG9906 study in Japan[3]. A study reported that 2%-7% of patients with ESCC achieved pCR after NAC; however, they included only a small number of cases[4,5]. Because of such response rates, recent studies have focused on assessing the efficacy of active surveillance to help avoid highly invasive esophagectomy[27]. In addition to the usual endoscopic diagnosis, which mainly involves biopsy, subsequent MDA reduction rate may allow the selection of endoscopic salvage resection instead of esophagectomy.

Our study had some limitations. First, it was a single-center study with a small sample size. The usefulness of EUS must be evaluated in the future by conducting larger prospective studies. Second, it was difficult to seamlessly match the sites measured before and after preoperative treatment with EUS. We attempted to match the measurement sites by recording the scope length from the mouth and comparing it to the surrounding vessels and structures. Third, the value of post-MDA could be different depending on the time since preoperative treatment. We assessed MDA 4 to 6 wk after the last preoperative treatment. However, to determine the effectiveness of neoadjuvant therapy and for active surveillance, it is necessary to examine the differences in MDA according to the time since treatment.

CONCLUSION

This study showed that ultrasound could not detect some residual tumors after neoadjuvant therapy. Meanwhile, focusing on the esophageal muscle layer as indirect findings rather than the residual tumor as direct findings could help diagnose the depth of the tumor. Applying these results in clinical practice may help clinicians provide more treatment options for patients with ESCC after neoadjuvant therapy.

ARTICLE HIGHLIGHTS

Research background

The diagnosis of endoscopic ultrasound (EUS) for esophageal cancer after neoadjuvant therapy is controversial. In addition, it is unclear whether the echogenic lesions detected using EUS are indeed residual tumors and how they appear on ultrasound.

Research motivation

There are few studies that contrast echographic and pathologic images of esophageal cancer after neoadjuvant therapy. In our clinical experience, we have observed that the esophageal muscle layer can be clearly visualized using EUS in patients with a good response to neoadjuvant therapy.

Research objectives

To investigate the ultrasound imaging features of residual tumors and identify the limitations and potential of EUS.

Research methods

Twenty-three patients receiving esophagectomy after neoadjuvant therapy [15 patients after

neoadjuvant chemotherapy (NAC) and 8 patients after chemoradiotherapy (CRT)] were studied. We diagnosed the T stage and compared ultrasound images with pathological findings using ultrasound for surgical specimens. Furthermore, the rate of reduction for the muscle layer defect was evaluated using EUS images obtained before and after neoadjuvant therapy.

Research results

The accuracy of T stage rate was 61%, which worsened after CRT (38%) than after NAC (73%). Moreover, pT0 could not be diagnosed in all cases. The detection rate of residual tumor for specimens using ultrasound retrospectively was 75%. Tumor borders were irregular and echogenicity was mixed type after CRT. There was a correlation between the pT stage and the rate of muscle layer defect reduction measured by EUS.

Research conclusions

Some tumors are undetectable on ultrasound when compared to pathological images. However, focusing on the esophageal muscle layer may improve the accuracy of T stage diagnosis of residual tumors.

Research perspectives

If EUS helps diagnose T stage of residual tumors in patients after neoadjuvant therapy by focusing on the muscle layer, the clinical treatment options can be expanded significantly.

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FOOTNOTES

Author contributions: Yonemoto S performed the research and wrote the paper; Uesato M came up with the study idea and supervised the study; Uesato M, Nakano A, Murakami K, Toyozumi T, Maruyama T, Suito H, Tamachi T, Kobayashi M and Kainuma S collected the data; Matsusaka K provided pathological advice; Matsubara H supervised the report.

Institutional review board statement: The study protocol was approved by Hospital of Chiba University Biomedical Research Ethics Committee, No. 3550.

Informed consent statement: Written informed consent was obtained before treatment for all patients.

Conflict-of-interest statement: All authors declare no conflicts-of-interest related to this article.

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CASE REPORT

Endoscopic ultrasonography drainage and debridement of an infected subcapsular hepatic hematoma: A case report

Theo Doyon, Thibault Maniere, Étienne Désilets

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Abstract

BACKGROUND

Endoscopic ultrasonography (EUS) has evolved in the last years making it not only a diagnostic modality but a therapeutic procedure. EUS is now used as an alternative technique to percutaneous and surgical drainage. Even though EUS is a challenging procedure and not always suitable compared to percutaneous drainage, there is a need for developing new therapeutic approaches to the liver for when percutaneous drainage is not feasible.

CASE SUMMARY

We present the case of a 82 years old male who developed an infected subcapsular hepatic hematoma (SHH) of the left lobe following percutaneous biliary drainage. After 2 failed attempts of percutaneous drainage of the SHH and because the patients couldn't withstand surgery, we conducted a EUS drainage and debridement of the SHH. Using a lumen apposing metal stent (LAMS) by a transgastric approach, we were able to gain endoscopic access to the SHH. With our experience in the debridement of walled off pancreatic necrosis using this technique, we were confident it was the right approach. After four debridement sessions, the computed tomography scan showed a clear regression of the SHH.

CONCLUSION

To our knowledge, this is the first case of successful endoscopic debridement of a SHH using a LAMS which appear to be feasible and safe in this specific case.

Key Words: Intervention endoscopic ultrasonography; Complication; Hepatic subcapsular hematoma; Transmural drainage; Lumen apposing metal stent; Case report

Core Tip: We conducted an endoscopic ultrasonography drainage and debridement of a subcapsular hepatic hematoma (SHH). Using a lumen apposing metal stent (LAMS) with a transgastric approach, we were able to gain endoscopic access to the SHH. With our experience in the debridement of walled off pancreatic necrosis using this technique, we were confident it was the right approach. After four sessions of debridement, the computed tomography scan showed a clear regression of the SHH. To our knowledge, this is the first case of successful endoscopic debridement of a SHH using a LAMS which appear to be feasible and safe in this specific case.

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INTRODUCTION

Endoscopic ultrasonography (EUS) has evolved making it more and more a therapeutic procedure[1-3]. For instance, it is now used for drainage of abscesses or hematomas when the first line of treatment that is percutaneous drainage is not feasible or has failed[1,4-7] or for gallbladder drainage for cases of refractory acute cholecystitis in the elderly who can't withstand surgery[8]. EUS is now used as an alternative technique to surgical drainage which is highly invasive, making EUS more favorable in term of procedural complications[1]. Percutaneous drainage, despite its high success rate also has its complications: Bleeding, perforation, peritonitis, fistula, sepsis and hematomas like subcapsular hepatic hematoma (SHH)[4,5,9]. Even though EUS is a challenging procedure and not always suitable compared to percutaneous drainage[5], there is a need for developing new therapeutic approaches to the liver when percutaneous drainage is not feasible[5] thus preventing the use of surgical drainage and its potential complications[1]. SHH can be a life-threatening situation[9-13]. SHH are traditionally managed conservatively with antibiotics and pain management[4,11,12,14]. However, when the SHH is persistent, becomes infected or worsens, it can be treated by percutaneous drainage and in case of failure by surgical drainage[4,5,13].

In walled off pancreatic necrosis (WOPN), debridement of the necrosis can be done surgically or by EUS which is less at risk of complications compared to conventional surgery[3,15,16]. The usual procedure for the drainage and debridement of WOPN is a puncture of the collection under EUS and dilation of the track using a cystotome or a balloon[15,16]. Endoscopic drainage of WOPN is then assured by the placement of multiple double pigtail stents or by installing a lumen apposing metal stent (LAMS) under EUS and use the stent as an access to get inside the necrosis for debridement of the WOPN[15]. Knowing that surgical drainage of SHH is an invasive and risky procedure, that the site of the hematoma can make percutaneous drainage difficult[1,4,5], that EUS drainage of a liver abscess is an effective and successful method to drain difficult to access abscess using a transgastric or transduodenal approach[4,5,7] and that EUS is used in debridement of WOPN[15,16]; we hypothesized that debridement of a SHH using EUS could be successful.

CASE PRESENTATION

Chief complaints

We report the case of a 82 years old male, known for a pancreatic cystic lesion under punctual surveillance by EUS.

History of present illness

The patient has a pancreatic cystic lesion under punctual surveillance by EUS.

History of past illness

The history of past illness are chronic kidney failure, hypertension, type 2 diabetes, dyslipidemia and coronary artery disease for which he took medication.

Personal and family history

None personal or family history.

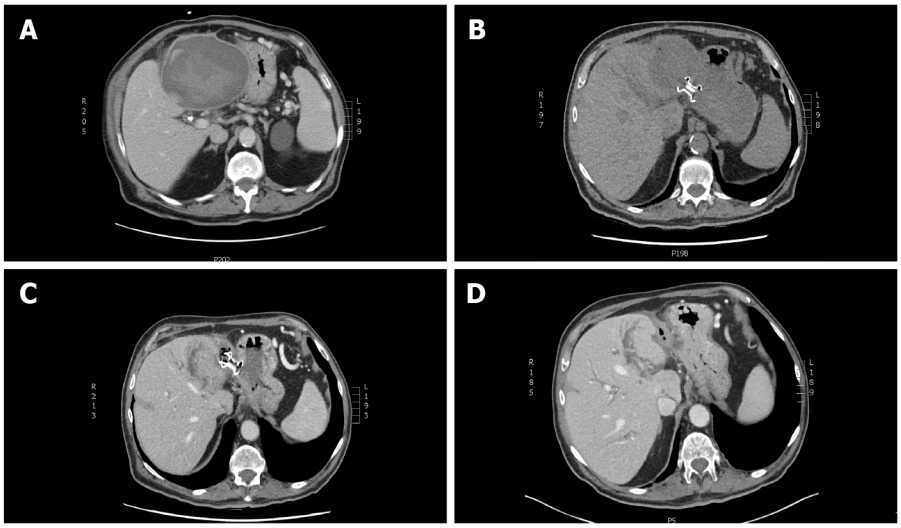

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Figure 1 Computed tomography scan of the upper abdomen showing the left subcapsular hepatic hematoma at different stages of endoscopic treatment. A: At diagnosis, the subcapsular hepatic hematoma (SHH) size was 12.5 cm × 10.5 cm × 12.5 cm and was compressing the stomach; B: At day 1 after endoscopic ultrasonography and lumen apposing metal stent (LAMS) was installed by transgastric approach; C: A month later, a control computed tomography (CT) scan of the upper abdomen showed a resorption of the SHH after 4 debridement sessions; D: Control CT scan of the upper abdomen after the LAMS was removed endoscopically.

Physical examination

During a routine monitoring of the pancreatic cystic lesion, EUS revealed a focal dilatation of the left intrahepatic bile duct.

Laboratory examinations

His laboratory tests showed white blood cells at 10.9 × 10^9/L, hemoglobin at 109 g/L, bilirubin at 23 μmol/L, alkaline phosphatase 231 U/L, aspartate aminotransferase 70 U/L, alanine aminotransferase 134 U/L and CA199 at 315 kU/L. Hours after the percutaneous drainage, the patient developed right upper quadrant pain and the hemoglobin level went down to 62 g/L.

Imaging examinations

Sequential endoscopic retrograde cholangiopancreatography was performed with cytology brushing and dilatation of a left intrahepatic biliary stricture followed by deployment of a 15 cm 8.5 Fr plastic stent in that area. A percutaneous drain in the left intrahepatic bile duct was then added in radiology.

FINAL DIAGNOSIS

The patient developed cholangitis.

TREATMENT

A control computed tomography (CT) scan revealed a 12.5 cm × 10.5 cm × 12.5 cm hypodense lesion compatible with a SHH in the left lobe (segment 3) (Figure 1). The patient was sent back in radiology and there was no active bleeding or pseudoaneurysm during the arteriography. Over the next days the patient developed a fever. A percutaneous 10 Fr catheter was inserted in the hematoma to attempt drainage and was repositioned once. Only a modest amount of bloody fluid was collected (150 mL). After a month of conservative treatment and a failed attempt to wean the patient from antibiotics, a control CT scan showed an expansion of the SHH with air bubbles within. Percutaneous drainage was again performed in radiology using a multiperforated 10 Fr stent and drained 100 cc of bloody liquid. Control CT showed a slow regression of the SHH and a thick wall around it.

Seeing the slow rate of resorption of the infected SHH, a consultation in hepatobiliary surgery was obtained but the patient was deemed too sick to withstand surgery. After consent from the patient, we decided to perform a EUS drainage of the infected SHH with a 10 mm × 15 mm LAMS (Hot-Axios, Boston scientific) by a transgastric approach under conscious sedation. The collection appeared heterogenous, surrounded by a thick wall and very close to the stomach smaller curvature. Considering the

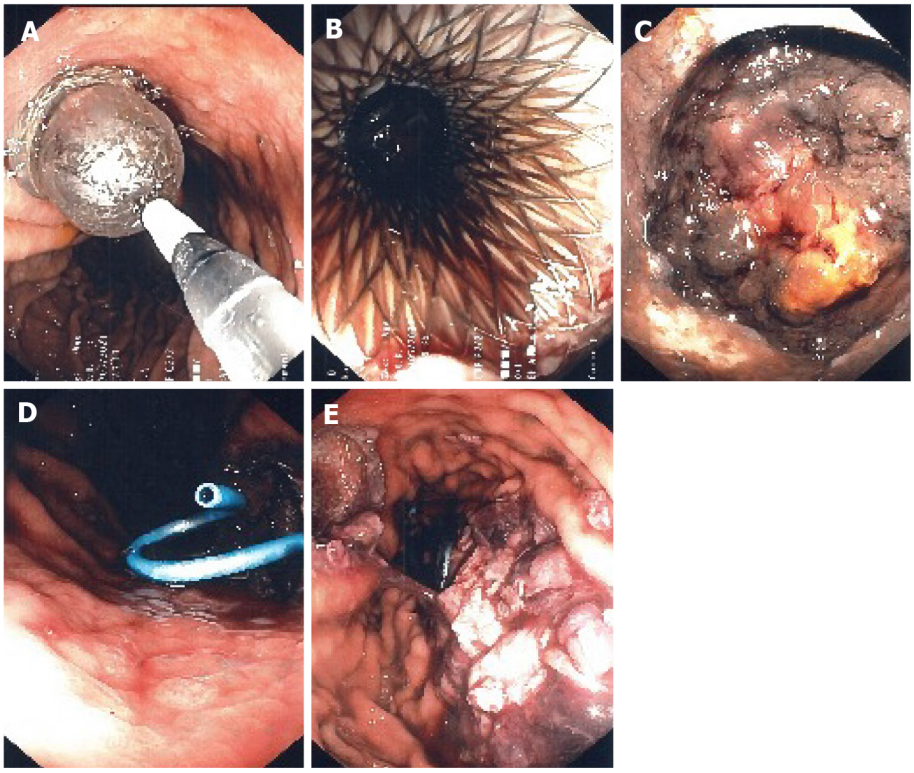

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Figure 2 Endoscopic ultrasonography guided transgastric insertion of fully covered 10 mm × 15 mm lumen apposing metal stent allows endoscopic access to the subcapsular hepatic hematoma for drainage and debridement. A: Dilatation of the lumen apposing metal stent (LAMS) was needed for the first debridement; B: Endoscopic image showing the LAMS after dilatation during the first of four debridements; C: Endoscopic image showing the subcapsular hepatic hematoma (SHH) during the second debridement; D: After each debridement, a double pigtail stent was inserted into the lumen of the LAMS allowing a more complete drainage of the SHH; E: Endoscopic image showing debris of the hematoma inside the stomach after the last debridement.

location of the SHH, the puncture was easy, and deployment of the LAMS was done using the standard Seldinger technique. Pus and blood were drained from the hematoma into the stomach immediately after deployment. After the procedure, the patient recovered well, with no adverse event. The two percutaneous drains were removed. The following day, the first of four debridement sessions under conscious sedation were performed with a standard gastroscope through the LAMS (Figure 2). Dilatation of the LAMS at 18 mm was needed at the first debridement. Each debridement session lasted between 30-35 min. Informed consent was obtained before each session. At the end of each debridement, a double-sided pigtail 7 Fr drain was installed inside the LAMS stent to help drain the SHH and maintain position and patency.

OUTCOME AND FOLLOW-UP

After the fourth debridement, the endoscopic appearance of the SHH cavity was clean with whitish walls and a CT scan revealed a massive regression of the SHH (2.2 cm × 3.1 cm); showing that the EUS procedure was a success. The LAMS was then removed endoscopically and the fistula between the stomach and the SHH closed immediately. The patient recovered well (Figure 3).

DISCUSSION

SHH is an "accumulation of blood between the Glisson's capsule and the liver parenchyma; rupture into the peritoneum has a 75% mortality rate"[10] which makes it life threatening[11]. In this case, the SHH was present for more than 3 mo, giving it time to organize itself and coagulate making it refractory to percutaneous drainage. Moreover, the SHH was infected, and the patient was under antibiotics for 6 wk without any success. Finally, the patient couldn't withstand surgery, so we had no choice but to try EUS drainage as a therapeutic procedure.

Important factors helped us choose this approach: The patient didn't have any coagulopathy; the encapsulated look and thick walls of the SHH; the anatomy of this region and the proximity of the SHH,

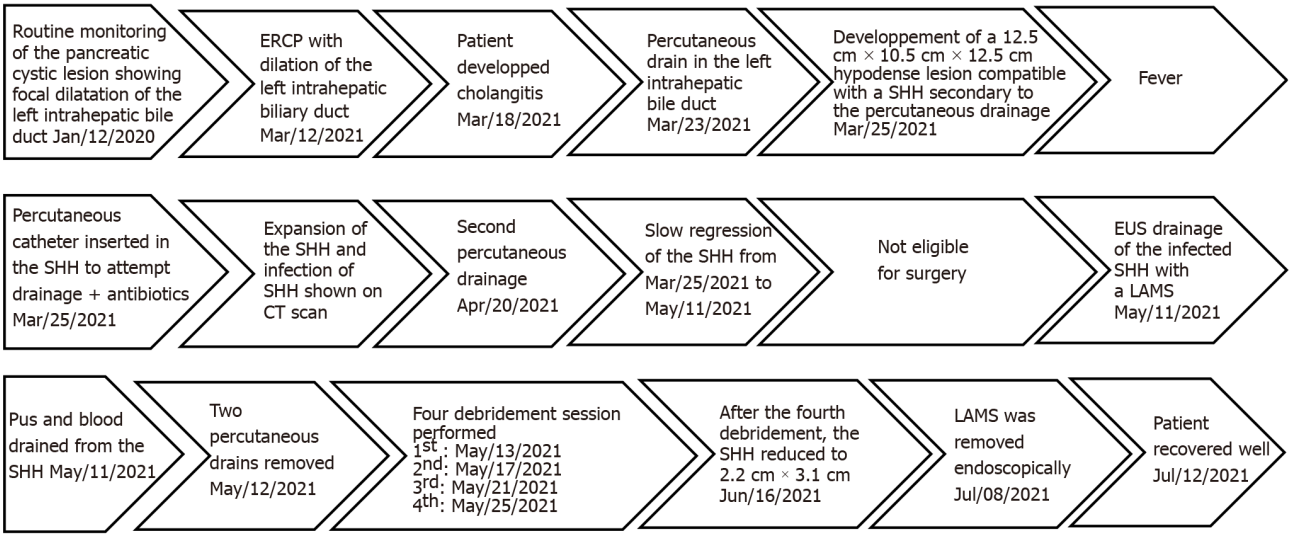

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Figure 3 Timeline of the medical care episode. CT: Computed tomography; SHH: Subcapsular hepatic hematoma; ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasonography; LAMS: Lumen apposing metal stent.

in segment 3 of the liver, with the small curvature of the stomach; the absence of pseudoaneurysm or active bleeding on the arteriogram and our experience in the debridement of WOPN. Altogether, it made us confident that EUS drainage and debridement under conscious sedation was the right approach. This way we were able to use a known and proven technique to a novel situation (*i.e.*, SHH). The procedure was a success, since after drainage and debridement, there was a significant reduction in the volume of the SHH (Figure 1).

This makes it the first EUS drainage and debridement of a SHH to our knowledge in the medical literature. We warn that this technique may be used only in cases where the collection is near the gastric or duodenal wall and when there is an experienced endoscopist who has competence in therapeutic EUS. The use of a naso-cystic tube to improve irrigation and shorten the resolution of SHH is debatable. Those tube are used also for common bile duct infection but are not well tolerated by patients. We decided to keep the LAMS in place for 2 mo to maintain the fistula wide open and make the access to the SHH easier. We removed it after the fourth debridement when the SHH was resolved. It is usually advised to remove those stents after 4-6 wk to avoid potential bleeding due to mucosal erosion[17].

There are many risks associated with the procedure. Aside from the general risks related to endoscopic anesthesia (respiratory failure, aspiration), the specific risk are bile leak, bleeding, infection, perforation, peritonitis and death. To assess and minimize the bleeding risk, doppler was used before the first endoscopic access to avoid any vascular structure in the gastric wall. The SHH was scanned with multiphasic acquisitions to rule out the presence of a pseudoaneurysm. If significant bleeding was to happen, we would have referred to angiography and arterial embolization. For peritonitis, the decision to send the patient to the operating room to proceed with conservative management would have been based on the severity and extent on imaging studies.

Furthermore, since the access to the SHH was in the smaller curvature, there was a potential risk of reflux of digestive flora into the SHH. This is a potential risk of all trans-gastric drainage techniques for which the consequences are unknown to our knowledge. Some have stated that it could be beneficial in the way that stomach acidity can provide a kind of chemical debridement [some even stop proton pump inhibitors (PPIs) between sessions of pancreatic necrosis debridement][18]; others fear potential supra-infection from the digestive flora and food relux from the digestive lumen[19]. In our case, the patient remained on large spectrum IV antibiotics from the first to the last endoscopic intervention to prevent supra-infection. PPIs were maintained.

We did not study the cost effectiveness of this approach compared to surgery. This is certainly an interesting question. Surgery remains for us the gold standard for refractory SHH; we proceeded this way because the risk of surgery was too high in our case. In the future, we think that EUS should be considered along the other modalities (surgery and radiological drainage) for the treatment of all kinds of peri-digestive infections (pseudocyst, pancreatic necrosis, liver and perihepatic abscesses, acute cholecystitis). The choice of the best modality should be based on available scientific data, specific risks for the patient, local expertise, and availability of the technology.

There are many potential advantages to the use of EUS: It is less invasive than surgery, there is no need for a transcutaneous tube or collecting bag, it can be a permanent drainage (*ex*: For gallbladders and pseudocyst) and larger stents allow for potential endoscopic debridement if needed. However, the lack of availability and expertise and the cost of material and technology make using EUS as a

therapeutical option challenging.

CONCLUSION

To our knowledge, this is the first case of successful endoscopic debridement of a SHH using a LAMS which appear to be feasible and safe in this specific case. Thus, EUS drainage of an infected SHH seems like an alternative therapeutic approach to consider, but clinical indications remain to be defined. More experience from other centers around the world will be needed before applying this treatment in a widespread fashion.

FOOTNOTES

Author contributions: Doyon T, Manière T and Désilets E contributed equally to this work.

Informed consent statement: The patient signed an informed written consent form for all the information that is found in this case report, and for all the procedures he went through.

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CASE REPORT

Intraoperative endoscopic retrograde cholangiopancreatography for traumatic pancreatic ductal injuries: Two case reports

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Abstract

BACKGROUND

In order to successfully manage traumatic pancreatic duct (PD) leaks, early diagnosis and operative management is paramount in reducing morbidity and mortality. In the acute setting, endoscopic retrograde cholangiopancreatography (ERCP) can be a useful, adjunctive modality during exploratory laparotomy. ERCP with sphincterotomy and stent placement improves preferential drainage in the setting of injury, allowing the pancreatic leak to properly heal. However, data in this acute setting is limited.

CASE SUMMARY

In this case series, a 27-year-old male and 16-year-old female presented with PD leaks secondary to a gunshot wound and blunt abdominal trauma, respectively. Both underwent intraoperative ERCP within an average of 5.9 h from time of presentation. A sphincterotomy and plastic pancreatic stent placement was performed with a 100% technical and clinical success. There were no associated immediate or long-term complications. Following discharge, both patients underwent repeat ERCP for stent removal with resolution of ductal injury.

CONCLUSION

These experiences further demonstrated that widespread adaption and optimal timing of ERCP may improve outcomes in trauma centers.

Key Words: Pancreatic ductal injury; Pancreatic leaks; Endoscopic retrograde cholangiopancreatography; Trauma; Endoscopic stenting; Case report

Core Tip: In the acute setting, intraoperative endoscopic retrograde cholangiopancreatography (ERCP) can effectively diagnosis and manage pancreatic duct (PD) injuries with stenting. At our high-volume trauma center, the on call therapeutic endoscopy team allows for quick and effective mobilization of resources. In this series, the time from admission to ERCP occurred within 6.3 and 5.6 h. The pancreatic injuries healed, and both stents were removed. In cases of traumatic PD injury, we believe that advanced gastroenterology care has the opportunity to improve the timing of diagnosis and treatment as a means to potentially reduce the morbidity and mortality associated with such injuries.

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INTRODUCTION

Pancreatic duct (PD) injuries are uncommon (occurring in 3% to 12% of traumas), primarily due its protective retroperitoneal location. They can be difficult to diagnose due to non-specific symptoms and delayed findings on imaging[1]. A delay in diagnosis can result in severe complications, such as a pancreatic fistula, hemorrhage, or abscess by which obtaining a fast and accurate diagnosis is paramount[2,3].

Standard therapy for high grade pancreatic injury with traumatic PD disruption is operative. As the duct itself is not amenable to repair, surgical options are resection and/or simple drainage accepting the inevitable pancreatic fistula. Major pancreatic resection is morbid and can produce nutritional cripples and render patients diabetic. Preoperative imaging is often inaccurate or not feasible. The limited sensitivity (52%) of computed topography (CT) is further complicated by timing, as CT scans performed in less than 24 h of presentation can often miss PD injuries as inflammatory associated changes are yet to manifest[1,4,5]. There is also poor sensitivity associated with magnetic resonance cholangiopancreatography (MRCP) imaging, and many times unstable patients may not be suitable for such imaging[4,6].

The diagnosis of PD transection is often suspected at the time of laparotomy. Knowing whether the PD is actually transected can be difficult. Visual inspection can over diagnose these injuries leading to unnecessary surgery. One would prefer to limit major pancreatic procedures to those patients with hemorrhagic shock or those without other options.

While endoscopic retrograde cholangiopancreatography (ERCP) is the most accurate method for assessing PD integrity and extent of injury, its wide spread use is hindered due to limited resources, local expertise and difficulty performing the procedure itself in an emergent, operative setting[1,7]. ERCP can also be therapeutic as PD stenting can be performed at the time of diagnosis. Stenting a duct that is transected can be challenging but if successful, the duct may heal around the stent and limit the need for major pancreatic resection. In this case series, we present two cases treated at a major urban trauma center where PD injuries were diagnosed with intraoperative ERCP and treated with sphincterotomy and stenting.

CASE PRESENTATION

Chief complaints

Case 1: Multiple gunshot wounds (GSWs).

Case 2: Blunt abdominal trauma.

History of present illness

Case 1: A 27-year-old male presented with four GSWs to the chest and abdomen.

Case 2: A 16-year-old female initially presented to an outside hospital with severe upper quadrant abdominal pain following blunt abdominal trauma. She remained at the hospital for two days with an inability to tolerate per oral intake, nausea, and vomiting.

History of past illness

Both patients had no specific history of past illness.

Personal and family history

No pertinent personal or family history of both patients.

Physical examination

Case 1: Upon arrival he was found to have penetrating GSWs to the left shoulder, left axilla, right flank, and subxiphoid areas.

Case 2: Upon arrival she was afebrile (37 ℃), normotensive (119/71 mmHg) but tachycardic (130 beats per min) with abdominal tenderness to palpation.

Laboratory examinations

Case 1: Labs on admission were notable for a white blood cell (WBC) count 10.9 K/mcL, hemoglobin 12.5 g/dL, platelets 430 K/mcL, international normalized ratio 1, aspartate transaminase (AST) 315, alanine transaminase (ALT) 282, alkaline phosphatase (ALP) 72, total bilirubin 0.2, amylase 127 units/L, lipase 59 units/L and lactate 6.8 nmol/L. He was resuscitated and imaging was obtained.

Case 2: Labs were notable for a WBC 16.6 K/mcL, Hg 11 g/dL, AST 23, ALT 12, ALP 74, total bilirubin 2.3 mg/dL, lipase 1160 units/L and amylase 441 units/L.

Imaging examinations

Case 1: Computed tomography angiography of the chest abdomen and pelvis revealed significant injuries, including but not limited to a left ventricle apex cardiac injury, laceration of liver lobe segments two and six, a pancreatic artery pseudoaneurysm (measuring 1.4 cm), and shrapnel wounds to the gallbladder, duodenum, pancreatic head, and hepatic flexure (Figure 1). There was no mention of pancreatic leak.

Case 2: A CT of the abdomen demonstrated a grade III pancreatic injury (thickness pancreatic transection involving the proximal tail and neck), large hemoperitoneum, and a 1 cm posterior splenic laceration for which she was transferred to our center for surgical care (Figure 2).

Further diagnostics

Case 1: He immediately went to the operating room (OR) for exploratory laparotomy where he underwent a non-anatomic bilateral liver resection, cholecystectomy, colon resection with end colostomy, gastric wedge resection, small bowel resection (20 cm) with anastomosis. He had a high-grade injury to his pancreatic head that would have required a Whipple to treat but it was not clear that he had a major PD injury. An intraoperative ERCP demonstrated a ventral PD leak in the head of the pancreas (Figure 3).

Case 2: She was sent directly to the OR, where an exploratory laparotomy revealed 500 mL of pancreatic ascites which was evacuated from the lesser sac and right upper quadrant. There was concern for PD disruption at proximal aspect of the pancreatic tail. An intraoperative ERCP demonstrated a PD leak in the body (Figure 4).

FINAL DIAGNOSIS

Both patients were diagnosed with PD leaks.

TREATMENT

Following the diagnostic ERCP, the first patient, underwent a pancreatic sphincterotomy followed by plastic pancreatic stent placement (5 Fr by 10 cm) (Figure 5). The main pancreatic duct (MPD) was intact. There were no technical challenges or associated complications from the procedure itself. The time from admission to ERCP was 6.35 h (Table 1). A drain was placed, and output decreased from 600 cc/d to 300 cc/d over two days. The drain amylase level was > 24000 units/L. Six days after the ERCP, his labs improved with an AST 46, ALT 77, ALP 89, and a total bilirubin 0.3. His hospital course was protracted related to non-pancreatic complications. He developed an intra-abdominal abscess communicating with the right abdominal wall wound. A CT abdomen pelvis did not show signs of a leak. However, he underwent a repeat ERCP with PD stent exchange to a larger 7 Fr by 10 cm plastic stent 18 d later due to a persistent leak on pancreatogram, with no further issues.

Similarly, in case 2, a 4 mm ventral sphincterotomy was performed followed by placement of a 5 Fr by 13 cm plastic stent into the dorsal pancreatic duct (Figures 6 and 7). There was no evidence of bile leakage. Her pancreas widely drained. The time from hospital admission to ERCP was 5.65 h. The procedure was technically successful with no adverse events. Her abdomen was left open. The next day,

Table 1 Patient characteristics with traumatic pancreatic duct leak

Patient	Age/sex	Etiology	Prior imaging	ERCP findings	Plastic biliary stent (Fr/cm)	Time from admission to ERCP (h)	Length of hospital stay
1	27/male	Gunshot wound	Yes, CTA	Ventral PD leak in the head of the pancreas	5/10 then upsized to 7/10	6.3	25
2	16/female	Blunt trauma	Yes, CT	Dorsal PD leak	5/13	5.6	22

CTA: Computed topography angiography; CT: Computed topography; ERCP: Endoscopic retrograde cholangiopancreatography; PD: Pancreatic duct.

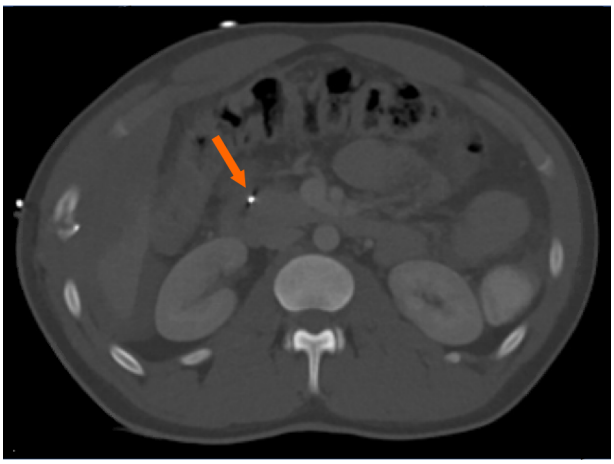

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Figure 1 Computed tomography of the abdomen demonstrating bullet shrapnel involving the proximal duodenum and the pancreatic head (arrow).

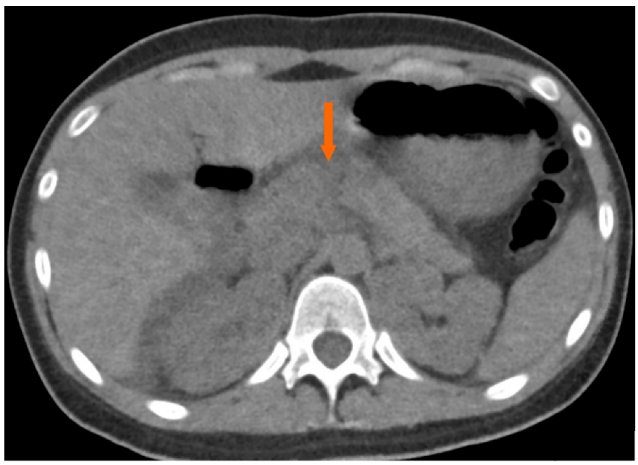

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Figure 2 Computed tomography of the abdomen revealing a full-thickness pancreatic transection involving the proximal tail and neck (arrow).

a MRCP confirmed placement of the pancreatic duct stent, which traversed the area of pancreatic transection with the tip of the stent residing in the tail of the pancreas. Two days after her initial surgery, she returned to the OR for abdominal re-exploration, pancreatic debridement, omentopexy, and primary closure.

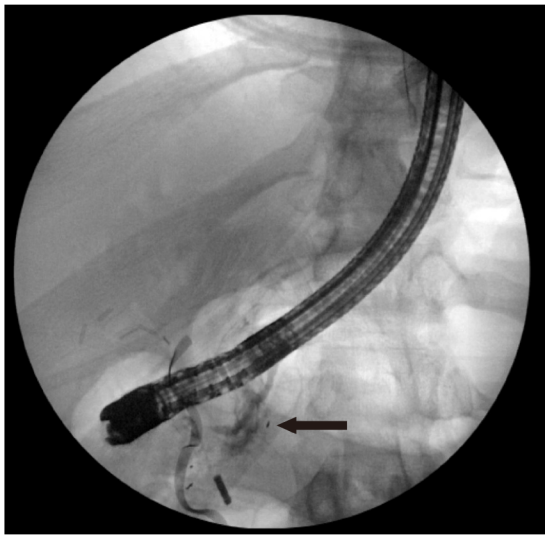

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Figure 3 Endoscopic retrograde cholangiopancreatography fluoroscopy showing a ventral pancreatic ductal leak in the head of the pancreas (arrow).

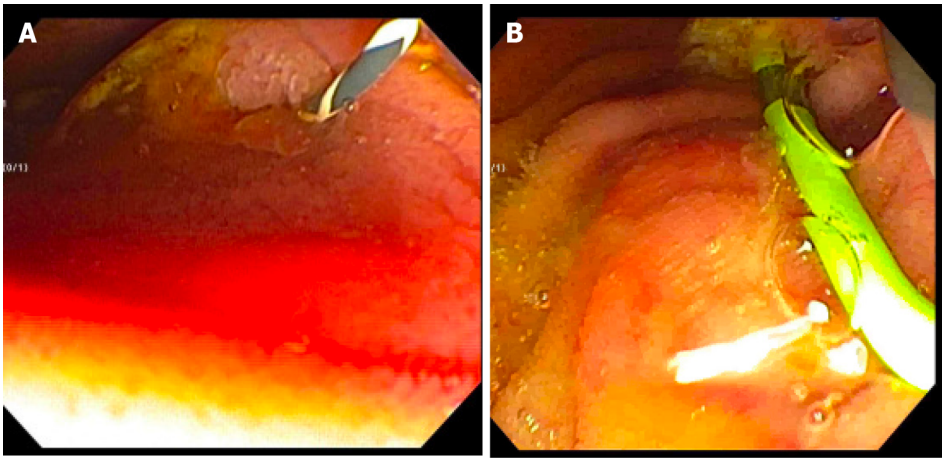

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Figure 4 Intraoperative endoscopic retrograde cholangiopancreatography. A and B: Endoscopic view following placement of an angled Visiglide wire into the ventral pancreatic duct (A) and placement of a plastic stent in the dorsal pancreatic duct (B).

OUTCOME AND FOLLOW-UP

Patient 1 was eventually discharged with a 25 d hospital length of stay. In the outpatient setting he underwent repeat ERCP with stent removal 84 d after discharge, with leak resolution and no further symptoms. The second patient's hospital length of stay was 22 d, and she was discharged without any major ERCP or pancreatic related complications. She underwent a repeat ERCP with stent removal 59 d following its initial placement with resolution of ductal injury.

DISCUSSION

This series demonstrates the efficacy, safety, and feasibility of intraoperative ERCP as a diagnostic and therapeutic tool. In this case series the average time from admission to ERCP occurred within 5.95 h. Both patients also underwent successful stent removal without any post-ERCP complications and resolution in the PD injury.

Clinical manifestations and management of PD leaks are largely dependent on the leak's size and location, where the integrity of the main duct influences prognosis[8]. In the setting of ductal injury, high pressure gradients cause pancreatic juices to flow outwards; as such, transpapillary stenting reduces the pressure gradient with preferential flow through the stent into the duodenum in order for

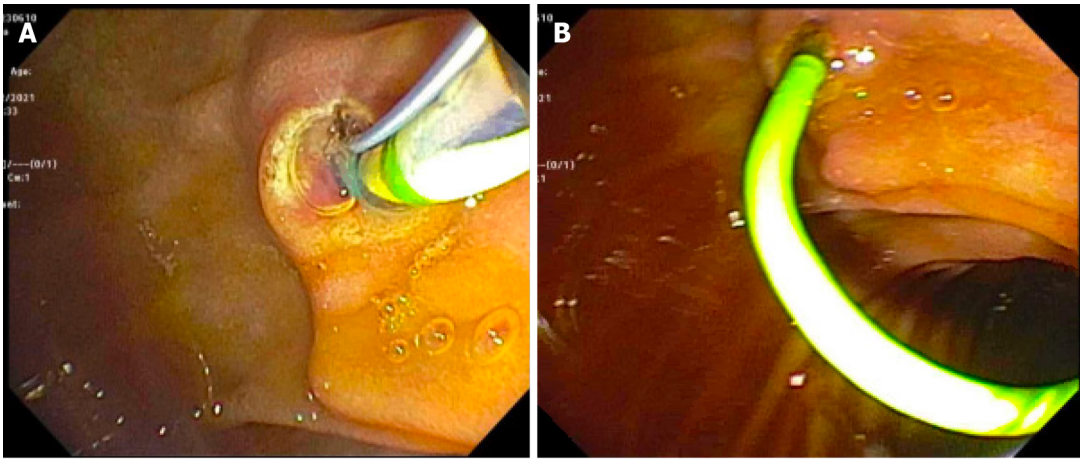

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Figure 5 Endoscopic view of the pancreatic sphincterotomy and pancreatic duct plastic stent placement. A: Pancreatic sphincterotomy; B: Pancreatic duct plastic stent placement.

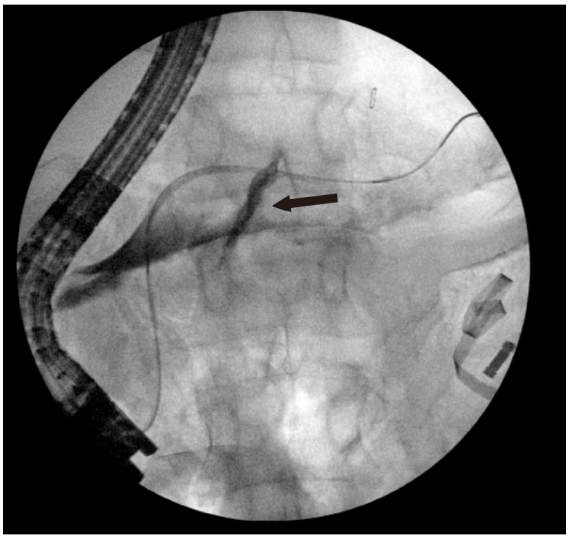

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Figure 6 Endoscopic retrograde cholangiopancreatography fluoroscopic view demonstrating a dorsal pancreatic ductal leak (arrow).

the injury to properly heal. At our center, we always perform a sphincterotomy with stent placement instead of employing nasobiliary catheter, with well documented success in cases of hepatic trauma as well[9].

The role of intraoperative ERCP in the trauma setting is not yet well defined. In a study of 71 patients with pancreatic injury, 50 of whom underwent immediate laparotomy, there was a 14% complication and 20% mortality rate[4]. In that study, intraoperative ERCP was not used. Instead, intraoperative visual inspection was undertaken to investigate for ductal injury. Four patients deemed not to have a leak developed pancreatic leaks with abscess formation. ERCP should be considered in the setting of traumatic pancreatic injury with a questionable PD injury. Its high diagnostic accuracy cannot be matched by any combination of a CT abdomen, serum amylase or peritoneal lavage[10]. In a large PD trauma series, an abdominal CT missed the diagnoses of major PD injury in 40.7% (11/27) of patients [11]. Furthermore, in a prospective study of 14 patients with PD injury, those undergoing ERCP greater than 72 h following trauma had higher rates of pancreatic complications and longer hospital stays[12]. In our series, both patients underwent ERCP immediately with no ERCP related complications or delayed lengths of hospital stays. One could postulate that early intraoperative ERCP effectively contained the leak and contributed to these positive outcomes.

ERCP with early stenting has also proven to be an effective and safe option in pediatric cases[13,14]. Yet, there has been some concern regarding the development of strictures, though it's unclear if such a complication occurs from the trauma itself or stent-induced changes[7]. In a small study analyzing long term outcomes for pancreatic stenting from blunt trauma the authors found that only 50% (3/6) of stents were successfully removed at 12, 19, and 39 mo[15]. Such complications were not seen in our patients,

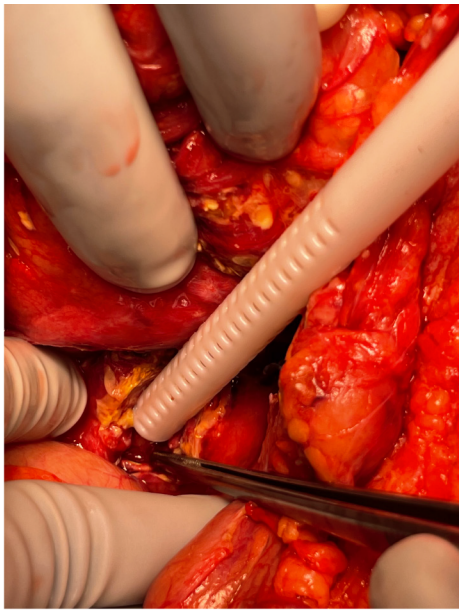

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Figure 7 Intraoperative photo confirming following placement of the pancreatic ductal stent.

likely because the stents were removed significantly earlier with minimal stent exchanges.

Studies exploring pancreatic trauma have not detailed intraoperative timing, which may be an important aspect for reducing complications as well. In a study of 43 patients with major PD trauma, 15 underwent stenting as the first treatment modality with a median time from trauma to ERCP of 6 d[12]. Within this group, there were 17 related complications including pseudocyst formation (8), PD stricture (4), distal pancreatic atrophy from injury site (3), and pancreatic fistulas (2). They also reported two deaths, one of which was related to severe pancreatitis where the stent was removed 8 d after insertion. The other death was attributed to a patient with severe alcoholic liver cirrhosis–unrelated to the stent. In another study of 48 patients with pancreatic trauma (26 blunt and 22 penetrating), the median time from presentation to ERCP was 38 d and only seven patients had a stent inserted for a pancreatic fistula (7) and a MPD stricture (1), whereby all patients avoided surgery[16]. While variable complications have been reported, the heterogeneity of presentations at different centers must be considered. The studies mentioned above did not employ, early intraoperative ERCP.

The logistics of performing intraoperative ERCP can limit its use, especially in cases of poly-trauma. Wise use of this novel technique requires commitment and flexibility from the surgeons and gastroenterologists. In instances of trauma, PD injury, duodenal injury and papilla edema may also increase the difficulty of the procedure itself, thereby increasing the chances of complications such as post-ERCP pancreatitis[17]. In both of our cases, there were no immediate or long term complications from the ERCP. Patient 1 did require upsizing from 5 Fr to 7 Fr stent, which is commonly seen. ERCP may be underutilized due to operator comfortability, lack of awareness of the value of endoscopic treatment in this setting, and equipment availability in the OR. Our high-volume trauma center is unique and is equipped to handle these situations with quick and effective mobilization of resources including on call therapeutic endoscopy.

CONCLUSION

In conclusion, this case series emphasizes the utility of intraoperative ERCP in cases of severe pancreatic trauma. Further studies are needed to clarify the optimal timing and safety outcomes in this setting.

FOOTNOTES

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LETTER TO THE EDITOR

Acute upper gastrointestinal bleeding: A stitch on time saves nine

Nishkarsh Gupta, Anju Gupta

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Abstract

Upper gastrointestinal bleeding is common and often needs timely intervention for optimal outcomes. Esophageal bleeding may occur due to local advancement of malignancy or bleeding from an arterio-oesophageal fistula. We discuss the management options available for such cases.

Key Words: Esophageal bronchial artery; Upper gastrointestinal bleeding; Bleeding; Fistula; Gastrointestinal

Core Tip: Esophageal bronchial artery fistula is a rare serious cause of upper gastrointestinal bleeding and needs to be managed appropriately. If unrecognized, it can be catastrophic. We discuss the management options for upper gastrointestinal bleeding due to these fistulas as a response to a previously published article.

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TO THE EDITOR

Acute upper gastrointestinal bleeding (UGIB) is a relatively common medical emergency with approximately 400000 cases/year and corresponding mortality rates of up to 16%[1]. In the index report, authors describe a rare case of UGIB due to an

esophago-bronchial artery fistula, in a patient with carcinoma of the esophagus with an esophageal metallic stent *in situ*[2]. The local advancement of the esophageal malignancy probably contributed to the UGIB as in this case the bronchial artery was non-aneurysmal.

Arterio-esophageal fistula (AEF) is a rare abnormal communication between the aorta and esophagus, with thoracic aortic aneurysm being the commonest association[3]. It can present as massive bleeding which can be potentially life-threatening. It is difficult to be diagnosed by endoscopy and therefore, requires a high index of suspicion. Another type of AEF is subclavian artery-esophageal fistula which has been previously reported in few patients with prolonged nasogastric intubation and such patients should be screened for the possibility of an aberrant aortic arch system to avoid this fatal complication [4,5].

Esophageal bronchial artery fistula is a rare serious cause of UGIB, which can be fatal if unrecognized. Bronchial artery aneurysm/pseudoaneurysm is commonly associated in such cases. Jadeja *et al*[6] reported a case of an esophageal-bronchial artery fistula due to pseudoaneurysm resulting from an endobronchial ultrasound-guided transbronchial needle aspiration. The case was successfully managed by endoscopic therapy and coil embolization.

Any patient with UGIB needs to be resuscitated with intravenous fluids, blood and blood products, vasopressors, and hemostatic agents as appropriate. In patients who become drowsy, confused, or hypoxemic, they would need prompt airway protection with endotracheal intubation to avoid aspiration and respiratory compromise. Antibiotics may be needed especially in patients with variceal bleeding and coexisting ascites or endocarditis.

Studies have shown improved outcomes with an urgent endoscopic management in the critically ill patients with hemodynamic instability or continuing transfusion requirements[7]. Urgent evaluation allows the identification of the type of bleeding, permits targeted therapy, and allows stratification of the sequelae of the bleeding which allows urgent risk stratification, and it also allows the early identification of the patients who would be suitable candidates for an early interventional radiological procedure or surgical intervention. In the index case also, since active bleeding was not seen on endoscopy, the patient could be further evaluated using computed tomography, which revealed signs of fistula between the bronchial artery and the esophagus. Even though there was no active bleeding, bronchial artery embolization was done as the signs of fistula formation were observed. Stent removal and re-stenting were done endoscopically along with embolization. Arteriography can provide a definitive diagnosis of source of bleeding and also yield temporary hemostasis by tamponade[4].

Endoscopy may be done under sedation or general anesthesia with endotracheal intubation depending on patient's sensorium and haemodynamic status. However, in the present report the mode of anesthesia has not been commented upon. Various nonoperative endoscopic hemostatic techniques have been recommended in cases where an active bleeding vessel can be identified as a source of UGIB. These treatment options include esophageal stenting, endoscopic fibrin application, injection therapy, thermal cautery, and endoclip application[8,9,10,11,12,13]. An epinephrine–saline solution injected in four quadrants surrounding the lesion is usually employed for endoscopic injection therapy. Mechanical hemostasis with hemoclips has been found effective for peptic ulcer bleeding with the advantage of minimal tissue disruption, leading to a likely faster ulcer healing. Recently, OverStitch (Apollo Endosurgery Inc., Austin, TX, United States) has been developed as an attractive minimally invasive device for endoscopic suturing which can potentially be useful for closing small perforations and fistulas without the need for surgical intervention[12,13].

Argon plasma coagulation is a technique which appears to be the most effective for broad ill-defined lesions such as vascular ectasias but also has been effectively employed in bleeding ulcer therapy[9].

Hemospray (Cook Medical, Winston-Salem, NC, United States) is a promising new therapy recently introduced for the management of UGIB. It is a hemostatic powder that acts as both a cohesive and an adhesive substance and thereby creates a mechanical barrier[10]. Cryotherapy has gained wider recognition particularly as a management modality for arteriovenous malformation. It allows for tissue destruction *via* freezing by nitric monoxide at a temperature of −89.5°C and creating an ice layer on the surface of the mucosa[9,11].

To conclude, AEF is a rare cause of UGIB and needs a high index of suspicion and interdisciplinary management. Minimally invasive endoscopic or interventional radiology treatment modalities are effective in managing the majority of such cases.

FOOTNOTES

Author contributions: Gupta N devised the concept, collected the data, revised the manuscript, and approved final version; and Gupta A collected the data, wrote the first draft, and approved the final version.

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ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

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MINIREVIEWS

Role of endoscopic ultrasound in vascular interventions: Where are we now?

Alessandro Fugazza, Kareem Khalaf, Matteo Colombo, Silvia Carrara, Marco Spadaccini, Glenn Koleth, Edoardo Troncone, Roberta Maselli, Alessandro Repici, Andrea Anderloni

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Abstract

From a mere diagnostic tool to an imperative treatment modality, endoscopic ultrasound (EUS) has evolved and revolutionized safer efficient options for vascular interventions. Currently it is an alternative treatment option in the management of gastrointestinal bleeding, primarily variceal type bleeding. Conventional treatment option prior to EUS incorporation had limited efficiency and high adverse events. The characterization and detail provided by EUS gives a cutting edge towards a holistically successful management choice. Data indicates that EUS-guided combination therapy of coil embolization and glue injection has the higher efficacy for the treatment of varices. Conversely, similar treatment options that exist for esophageal and other ectopic variceal bleeding was also outlined. In conclusion, many studies refer that a combination therapy of coil and glue injection under EUS guidance provides higher technical success with fewer recurrence and adverse events, making its adaptation in the guideline extremely favorable. Endo-hepatology is a novel disciple with a promising future outlook, we reviewed topics regarding portal vein access, pressure gradient measurement, and thrombus biopsy that are crucial interventions as alternative of radiological procedures. The purpose of this review is to provide an update on the latest available evidence in the literature regarding the role of EUS in vascular interventions. We reviewed the role of EUS in variceal bleeding in recent studies, especially gastric varices and novel approaches aimed at the portal vein.

Key Words: Endoscopic ultrasound; Cyanoacrylate; Coil injection; Gastric varices; Gastrointestinal bleeding; Vascular endoscopic treatments

Core Tip: Currently endoscopic ultrasound (EUS) is an alternative treatment option in the management of gastrointestinal bleeding, primarily variceal type bleeding. This manuscript tackles a comprehensive review for the uses of EUS in the majority of vascular interventions with regard to gastrointestinal bleeding and offers a directive for the technical aspects in carrying out a procedural treatment of combination coil and glue therapy for gastric varices.

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INTRODUCTION

The endoscopic ultrasound (EUS) technology has dramatically evolved since its conception in the 80s, transforming from a supplementary add-on of the diagnostic process to a core modality in the diagnosis and therapy in a wide range of diseases[1]. EUS diagnostic capability has evolved immensely in recent years primarily enhancing fine needle aspiration (FNA) and fine needle biopsy, the acquisition of particularly gastrointestinal (GI) and pancreato-biliary lesions, providing cytohistologic sampling[2]. Having the diagnostic sensitivity of 85% to 95% in detecting malignant pancreatic tumors and specificity of 100%, EUS guided FNA is being regarded as a main staple if not a gold standard by many experts[1]. Further extending the reach towards lesions of the pancreas, mediastinal adenopathy, GI tract submucosal lesions and retroperitoneal masses, EUS provides a detailed image and obtains tissue samples in a minimally invasive manner that is safe and accurate for diagnosis[3,4]. On the other hand, therapeutic EUS-guided drainage is a favored option in the management of pancreatic fluid collections, biliary and gallbladder diseases[5-7]. Moreover, the indications for interventional EUS grow more and more having nowadays a central role in the management of biliary diseases in altered anatomy, gastric outlet obstruction and post-surgical abdominopelvic fluid collection drainage[8-11].

Under the scope, focusing on various GI conditions, initially EUS provided clinicians with valuable information pertaining to clinical and anatomic information. Aspects such as the appearance, size and location of a structure indicated variable descriptive factors regarding a plethora of conditions[12]. Due to the proximity of the GI system to vascular structures, EUS today can provide precise interventions that target inaccessible, or less accessible surrounding vascular sites[12]. EUS has advanced as alternative treatment option in the management of GI bleeding providing an efficient treatment modality and offering fewer adverse events (AEs). Effective treatment options that are EUS guided exist, such as sclerotherapy, tissue adhesive injections, and coil embolization. Recently, the employment of glue injection and coil embolization techniques with EUS seem to be thriving in clinical practice. Stand-alone therapy options present with variable risk factors and complications, ultimately delegating to clinicians and technicians in the field to utilize a combination of both glue injection and coil embolization under the guidance of EUS[13]. The purpose of this review is to provide an update on the latest available evidence in the literature regarding the role of EUS in vascular interventions.

TECHNICAL FEATURES

Primarily, prior to the promotion of EUS, definitive understanding of the technical strengths and limitation it encompasses is key to its adoption into clinical practice. First and foremost, EUS provides precise targeting of vascular structure in direct proximity for the GI wall (Figure 1A). It further allows visualization reducing the risk of injection out of site[12]. It is also worth mentioning, the precision regarding biopsies of tissues is much higher than the conventional method. Furthermore, EUS provides a sort of 'check-up' following procedures such as the obliteration of a varix, that grants validity for a clinician achieving technical success. Conversely, nothing is without limitations and EUS is not short of either, ultrasonography remains to have a steep learning curve. Additionally, following the transmural access into deeper tissue, bleeding from the extra-luminal side is not accessible by endoscopy, causing

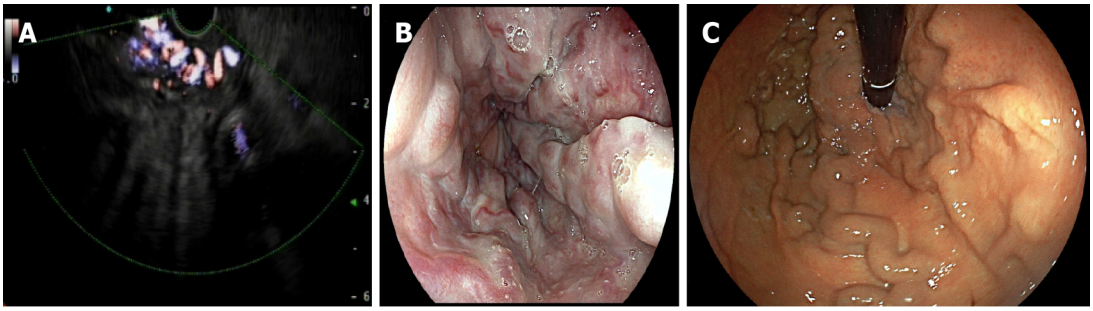

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Figure 1 Endoscopic images. A: Endoscopic ultrasound-Doppler detecting gastroesophageal varices; B: Endoscopic view of large esophageal varices (classified as grade 2 at Westaby classification)[19]; C: Endoscopic view in retroversion of gastro-esophageal varices (classified as gastroesophageal varix 2 at Sarin classification)[22].

urgent surgical or radiological therapy. Likewise, AEs exist with the use of EUS, although at a much lower rate than the conventional therapy, the risk still exists and may be fatal. The caliber of the EUS aspiration channel is restrictive and multiple predicaments arise[14]. Firstly, luminal contents may not be aspirated creating artifacts that hinder the sonographic image during the procedure. Secondly, the reduction in caliber size limits the apparatus from removing blood clots that not only obstruct the view but may lead to further thromboembolic events that may be fatal[15]. A larger range of accessories and devices designed for ultrasonography, miniature apparatus, correct antibiotic prophylaxis may tackles some of the limitations mentioned. Ultimately the standardization of a technique of injection, volume of injection, size of coils, and speed of injection are challenges to confront while adapting a universal methodology for any EUS-guided procedure[15].

Initially, a prior conventional endoscopic examination is necessary to confirm varix type and concomitant esophageal varices with gastric varices. The procedure should be performed with the patient under deep or conscious sedation, according to each institution protocol. Using a linear echoendoscope for the evaluation of varix size and treatment evaluation is the mode of choice[16]. Once the varix is identified under EUS, it is necessary to characterize the total diameter of the widest varix which should be punctured by a 19G needle[17]. It is important to choose the size of the coil depending on the size of the widest varix. More importantly, the size of the coil should not exceed the caliber of the vessel it is injected into. In case of glue injection, following the deployment of the coil, 2 mL of distilled water followed by 0.5 mL of N-butyl-2-cyanoacrylate, followed by another 2 mL of distilled water was injected and then the needle removed[17]. Lastly, EUS with Doppler flow is important for technical success evaluation. The presence or absence of flow within the varix is what is evaluated[6,16,17].

TYPE OF BLEEDING

Variceal bleeding

Variceal bleeding is known to be the most feared lethal complication of portal hypertension. Whilst gastric varices tend to be the most problematic; esophageal, rectal, and other ectopic locations present with serious complications. As described in further detail below, guidelines offer a wide range of therapeutic options depending on location of the varix, whether offering standard endoscopic, surgical, or interventional radiologic therapies, each come with strengths and weaknesses. While centering our focus on standard endoscopic treatments, we find major limitation in the addressed therapies, whether it's a matter of severe AEs and high risk or a high recurrence rate of the varix rebleeding and a low clinical outcome. Under EUS guidance, coincidentally due to higher precision of vascular targeting, the treatment options deemed more efficient with an overall higher success rate and clinical outcome[18]. Furthermore, the recommendation enclosed reports that EUS is a feasible safe option for patients who were unsuccessful candidates for conventional therapies[18].

Variceal classification

Different classifications for esophageal varices have been created, to mention a few: Dagradi, Conn's, Paquet's, Westaby, Calès and Soehendra[16]. The most used one are the Westaby and Dagradi's classification.

Westaby's offers a three-grade system classification of identifying the progression of esophageal varices classified as[19]: Grade 1 varices appearing as slight protrusion from the mucosa, which can be depressed with insufflation [20]; Grade 2 varices occluding less than 50% of the lumen (Figure 1B); Grade 3 varices occupying more than half of the lumen and are extremely close to one another with a confluent appearance.

Alternatively, the Dagradi classification is a five-grade system for esophageal varices classifieds as [20,21]: Grade 1 varices less than 2 mm in diameter that are linear or sigmoid in shape and appear with compression of the wall with the scope, they usually present as blue or red in color; Grade 2 are blue varices sized between 2-3 mm in diameter and are mildly tortuous or straight and elevated; Grade 3 are blue tortuous or straight varices sized between 3-4 mm in diameter; Grade 4 are varices larger than 4 mm that surround the esophageal lumen and are closely neighboring each other around the wall with or without mucosal cover; Grade 5 are grape like varices that occlude the lumen and present as red varies overlying blue varices; 'varices over varices.

Similarly, the most used classification for gastric varices is the 'Sarin's' classification[22]. Four different types based on their location in the stomach are classified as two types of gastroesophageal varix (GOV) and two types of isolated gastric varix (IGV)[23]. Type GOV1 are varices that extend in the cardia to lesser curvature of the stomach. Type GOV2 are varices that extend from the cardia towards the greater curvature of the stomach, terminating at the gastric fundus (Figure 1C). Type IGV1 are varices in the gastric fundus that do not extend to the esophagus. Type IGV2, also referred to as ectopic gastric varices occur in other parts of the stomach. To a certain degree many clinicians regard esophageal varices and type GOV1 as gastroesophageal varices whilst GOV2 and IGV1 are fundal varices[20,23].

ESOPHAGEAL VARICES

Esophageal variceal bleeding is much more common than gastric varices, with high morbidity and mortality but fortunately carries less detrimental complications. In essence esophageal varices is a collateral circulation that develops due to portal hypertension[13]. Esophageal varices hemodynamics differ from patient to another, thus making their treatment problematic[14]. Guidelines state that first line treatment of esophageal bleeding is to be treated by endoscopic band ligation followed by transjugular intrahepatic portosystemic shunt (TIPS) or endoscopic sclerotherapy, both pose significant risk to the patient[12]. Endoscopic preventative bleeding measures for esophageal varices include endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL)[18]. Primarily EIS, a much older technique, involved the embolization of the feeder veins by injecting a sclerosing agent that maintained the regression of the collateral circulation. Thus, by inhibiting the hemodynamics of the varices' the recurrence remained low[24]. Unfortunately, the complexity of delineating the circulations hemodynamics and the high complication risk associated, EIS remains a challenging option for the treatment of variceal esophageal bleeding. In efforts to a more effective treatment with less complications, EVL was developed[24]. EVL as the name suggests ligates the varices and thus blocks the flow of blood in the collateral area. Since the technique doesn't target the feeder vessel, recurrence rate is high. In hindsight EVL's main limitation is the lack of clinical and anatomical information on the hemodynamics of the circulation and the feeder vessel[25]. On the other hand, EUS provides a selective safe effective treatment option that can predict variceal recurrence, estimate the circulation's hemodynamics, and provide follow-up screening and management[26]. A study with the aim of studying the relationship of both treatments (EVL and EIS) recurrence used 3D-EUS and defined four main variceal circulation patterns as: cardial inflow without paraesophageal veins, cardial inflow with paraesophageal veins, azygos-perforating pattern, and a complex pattern. The study concluded the use of EVL to be limited to collaterals running parallel to the varices whilst sclerotherapy to be used for paraesophageal veins with a larger diameter and a perforation pattern[18]. Furthermore, the utilization of EUS technology provided effective directed treatment option of pattern types that aided a successful clinical outcome[27]. Moreover, in one study that utilized a sclerosing agent targeted under EUS guidance, an average of 2 to 3 sessions required to achieve complete obliteration. The study further reported in their cohort of 5 patients; no bleeding recurrence or death and one patient developed an esophageal stricture that was treated with balloon dilation[28].

GASTRIC VARICES

Standard therapy for gastric varices by current guidelines recommends the use of endoscopic cyanoacrylate (CYA)[29]. High bleeding rates and fatal AEs mandates the need for a more feasible option such as EUS guided. EUS-guided therapy provides high technical success and an overall better safety profile [24,29]. Romero-Castro *et al*[30] in a retrospective analysis that aimed at a direct comparison of the variable EUS-guided methods showed similar obliteration rated of gastric varices in both CYA injection and coil embolization (Table 1). Mohan *et al*[18] carried a meta-analysis that presented that the combination of EUS-coil/CYA had significantly fewer instances of gastric varices recurrence than EUS guided CYA injection (5.2% *vs* 15%). Furthermore, McCarty *et al*[31] reviewed a meta-analysis of 11 studies compared EUS-guided methods and discovered similar advantages to the combined approach. Their results showed that EUS-coil/CYA had a significantly higher rate of GV obliteration than either EUS-CYA (98% *vs* 96%) or EUS-coil (98% *vs* 90%). Moreover, the combination of EUS-coil/CYA had a

Table 1 Comparison of the main studies reporting data of endoscopic ultrasound guided treatments for gastric varices

Ref.	Study design	Number of patients	Technical success	Clinical success	Adverse events
Romero-Castro *et al*[30], 2013	Retrospective analysis of a prospectively maintained database	30 total patients, 11 ECA, 19 CYA	27/30 (90%)	18/19 (96.7%) CYA; 10/11 (90.9%) ECA	40% total AEs; CYA 11/19 (57.9%); ECA 1/11 (9.1%)
Lôbo *et al*[17], 2019	Randomized Controlled Trial	32 total patients; 16 ECA + CYA, 16 CYA	-	-	Early AEs: 8 (50%) ECA + CYA; 10 (62.5%) CYA. Pulmonary embolism: 4 (25%) ECA + CYA; 8 (50%) CYA
Robles-Medranda *et al* [29], 2019	Randomized Controlled Trial	60 total patients, 30 ECA + CYA; 30 ECA	60/60 (100%) in both groups	ECA + CYA 30/30 (100%), ECA 27/30 (90%)	ECA + CYA 2/30 (6.7%); ECA 1/30 (3.3%)
Bazarbashi *et al* [16], 2020	Prospective Study	40 total patients; 10 ECA, 30 CYA	10/10 (100%) ECA; 29/30 (96.7%) CYA	10/10 (100%) ECA; 26/30 (87%) CYA	10% ECA; 20% CYA

ECA: Endoscopic coil application; CYA: Cyanoacrylate; AE: Adverse event.

lower recurrence rate than their singular respective modalities. The combination modality had lower rebleeding rate and frequency of AE than EUS-CYA[29,32]. Data indicates that EUS-guided combination therapy of coil embolization and glue injection has the higher efficacy for the treatment of varices. Similarly, another interesting study reported that although combined therapy had a superior safety profile over EUS-guided CYA injection, when compared to EUS coil injection similar results were obtained[29]. However, an interesting notion to point out is that coil embolization is technically demanding when compared EUS- guided glue injection[14]. In efforts to reassess a proper direction for the leading choice of treatment, multiple factors come into play. Evaluating technical success, AEs, recurrence rate and clinical outcomes shape the best decision in moving forward[14].

A meta-analysis and systematic review that aimed to evaluate the effectiveness of the above-mentioned outcome measures, studied comparative groups of mono and combination modalities[31]. Overall technical success, clinical success, and AEs for EUS treatments was 100%, 97% and 14%, respectively. Moreover, EUSguided CYA + coil embolization resulted in a better technical and clinical success compared to CYA alone (100% *vs* 97% and 98% *vs* 96%) and coil embolization alone (99% *vs* 97% and 96% *vs* 90%)[18]. Similar results coming from a single center observational study outlines primary preventative prophylactic treatment of gastric varices and the use of combination EUS of coil and CYA glue injection as the preferred modality achieving 100% technical success, 96.7% gastric varices obliteration on EUS confirmation and post-treatment recurrence was at 2.5% and AEs at 4.9%[33].

EUS further provides an advantage in the use of CYA injection in the obliteration of gastric varices as an overall lower mean volume of the glue is needed to reach similar technical success with the same safety profile of rebleeding rates being (8.8% *vs* 23.7%)[32]. One study mentioned less incidence of pulmonary embolism for EUS guided coil embolization when compared to EUS CYA therapy[29]. Coil based therapy for the treatment of gastric varices was reported to be superior to traditional endoscopic therapy with CYA injection[16]. In another study, EUS guided coil therapy exhibited high technical success rates, low AE rates, superior time to rebleed, time to repeat transfusion, and time to repeat intervention when compared to endoscopic CYA injection[16]. The study further concluded that the rate of rebleeding in the CYA arm was 38% which was higher than what was that literature 20%-30%. A single center parallel RCT studied efficacy and safety of EUS-guided coil embolization and CYA injection *vs* EUS-guided coil embolization alone in the managing gastric varices. Interestingly, the immediate disappearance of varices was observed in 86.7% of patients treated with coils and CYA, *vs* 13.3% of patients treated with coils alone indicating the combination therapy to offer an immediate surveillance feature within the procedure. Likewise, the combined treatment, had 83.3% of patients free from reintervention when compared to coil alone 60%[34]. One study reported no statistical difference between EUS guided coils plus CYA *vs* conventional CYA technique in relation to the incidence of embolism. The study concluded a larger tendency of patients to develop embolism when compared to the conventional endoscopic technique without EUS[18]. With regards to the choice of tissue glue/adhesives, CYA, one study aims to evaluate the safety in applying EUS-guided modality of hydro coils in gastric varices. Hydro coils are coils coated with different types of expandable hydrogel polymers, causing rapid occlusion of vessels, and favoring thrombus formation. The study reported fewer recurrences 8.6% and no differences with regard to side effects when compared to CYA[31].

ECTOPIC VARICES

Following the recommendation of current guidelines, endoscopic band ligation and glue injection are

the established techniques for managing ectopic variceal bleeding[18]. One example are duodenal varices, common in end-stage patients with decompensated cirrhosis, current treatment options include TIPS, endoscopic band ligation or sclerotherapy. Commonly patients presenting with duodenal varices are referred to endoscopic treatment for bleeding prevention and EUS guided situates the clinicians technical outcome at an advantage[35]. EUS provides superior characterization of the variceal complex and offers higher obliteration with a lower recurrence rate in compared to the conventional treatments. Thus, offering a feasible safe option to manage these patients[14].

Rectal varices are a well-recognized complication of portal hypertension[36]. The perforator vein supplies the variceal circulation, which invaginates superficially and bleeds. Common treatment options include interventional radiology and surgery with a mortality rate documented as high as 80%[36]. Well regarded recommendation in a previous study showed that the injection 2 mL of N-butyl 2-CYA into the varix, thrombosed the collaterals and bleeding subsided in 2 wk[37]. In attempts to further reduce conventional interventional radiology mortality rates in the treatment of rectal varices, a study suggested the added benefit of EUS-guided treatment that provides an overall better diagnostic approach and higher technical success in targeting the perforator vein directly thus achieving homeostasis with less coils and hence overall less AE rates[36].

Additionally, most of the literature evaluating EUS guided techniques focus on upper GI bleeds. One study reported overall clinical outcome success in patients with rectal bleeding in all mono and combination modalities[37]. Authors recommend targeting the feeder vein in patients referred for endoscopic management if unfit for surgical or interventional radiological treatment[37]. Likewise, duodenal ectopic varices usually present in patients with end-stage liver disease, which are referred for endoscopic treatment to prevent bleeding. In one study authors recommended EUS-guided interventions, specifically combined therapy as it offers a superior complete obliteration rate to monotherapy[35].

Non-variceal bleeding

Upper GI bleeding not attributed to varices is common having multiple etiologies, peptic ulcer disease, erosive diseases, Mallory-weiss syndrome, Dieulafoy's lesions, gastric antral vascular ectasia, peripancreatic pseudoaneurysm and others (Figure 2). Definitive management measures involving EUS-guided therapies provide a novel treatment option with optimal efficacy. As a result of the steep learning curve and the need of extensive training programs in endosonography, EUS-guided angiotherapy for acute GI bleeding is limited to tertiary centers. EUS-guided management of non-variceal upper GI bleeding is an innovative option especially in cases of recurrence. Simultaneous characterization of the bleed and intra-procedural ensuring of therapy effectiveness provides an extra edge in comparison to conventional therapy[15]. That being said, literature on the matter is limited and no randomized controlled trials are available. Further studies need to clarify efficacy and safety in larger robust trials.

PSEUDOANEURYSM EMBOLIZATION

Pseudoaneurysms are blood collections that surround injured tissue, commonly known as false aneurysms and differ from true aneurysms, which form a blood-filled sac and bulge from the vessel wall[38]. With a prevalence of 0.04-0.1%, pseudoaneurysms are commonly associated with the splenic artery. Importantly, pseudoaneurysms usually occur following abdominal infections or post-pancreatitis[39]. Pseudoaneurysms are asymptomatic in most cases and usually appear as an incidental finding on radiological graphs. Due to the detrimental high rupture risks of up to 20%, allow for EUS-guided therapy to be an effective option for patients[40]. Many case-reports and series outlined good outcomes with obliteration of pseudoaneurysm following EUS-guided treatment, as reported by Mann *et al*[27], in a recent review of the literature. Recently, one study by Rai *et al*[41], aimed to study EUS-guided glue and coil injection in six patients who failed angiographic embolization of splenic artery pseudoaneurysm. Complete obliteration was achieved in all patients with larger aneurysms, requiring a 'larger' injection of coils and glue (1-2 mL). Moreover, no AEs occurred in any of these patients. Looking forward, this may provide an effective technique for the treatment of pseudoaneurysm in different abdominal segment accessible under EUS-guidance. Table 2 outline technical features from case report series on therapeutic management of pseudoaneurysms under EUS-guidance.

ENDO-HEPATOLOGICAL INTERVENTIONS

Nearing the last decade, a sub discipline of endoscopy named "Endo-hepatology", was introduced. In an aim to move towards a more accurate diagnosis, former procedures such as diagnostic biopsies and pressure measurements were advanced. Body habitus always posed as a challenging limitation whilst performing a biopsy of the liver however, using EUS, circumventing this problem became feasible and furthermore, simultaneous bi-lobar biopsies were possible[42]. EUS also improved patients' perception

Table 2 Case reports on endoscopic ultrasound-guided treatment of pseudoaneurysms

Ref.	Design	Technical success (%)	Adverse events	Recurrence	Needle size	Treatment
Robb *et al*[61], 2012	Case Report	100	None	None after 5 mo follow-up	19G	Psuedoaneurysm embolization
Gamanagatti *et al* [62], 2015	Case Report	100	None	Recurrence; asymptomatic	22G	Thrombin injection 300-500 units
Mann *et al*[27], 2017	Case Report	100	Not reported	None after 2 wk follow-up	19G	5 coils of 10 mm size were placed, 3000 units of thrombin injected
Jhajharia *et al*[63], 2018	Case Report	100	Not reported	None in all three patients	Not reported	1000 units of thrombin
Gunjan *et al*[63], 2018	Case Report	100	Not reported	None after 9 mo follow-up	19G	3 mL of undiluted N-butyl-cyanoacrylate
Sharma *et al*[65], 2019	Case Report	100	None	Full obliteration on 2-wk follow-up	19G	Five 10 mm coils placed, 6 mL of 3000 units of thrombin injected in six boluses of 500 units each

G: Gauge.

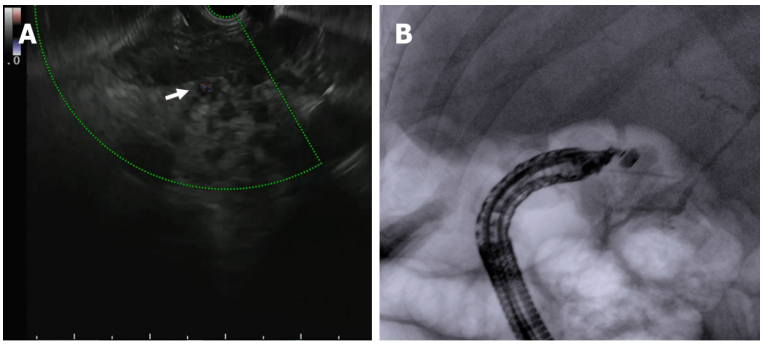

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Figure 2 Embolization of the gastroduodenal artery with cyanoacrylate glue due to active bleeding. A: Ultrasound view of the gastroduodenal artery (arrow); B: Fluoroscopic view of the gastroduodenal artery.

of undergoing a biopsy, due to the decreased recovery time and better tolerance overall. The added benefit did not revolve around technical expertise, as previous options required less technical training. The advantage lies with the reduction in sampling error due to the bi-lobar biopsies[42]. Additionally, EUS biopsies can be concurrently carried out with portal pressure measurements in a singular procedure, providing a more appealing option to patients than the trans-jugular approach. That anatomic proximity of the stomach and duodenum to major vascular structures, make EUS a vital technique in accessing structures such as the portal vein (PV). Existing applications of PV interventions using EUS include sampling, embolization, thrombolysis, and stent placement[27].

PV interventions: Sampling, pressure measurement and embolization

Circulating tumor cells (CTC) in the PV offer a positive predictive value of liver metastasis from pancreatic and colorectal cancers. The sampling of CTC under EUS guided access is vital, as CTC are more prevalent in the PV than in the peripheral blood. This provides an advantage with EUS, in order to sample tumor cells for further analysis[43]. The first report of EUS-guided PV sampling was in 2015, followed by another study in 2017 that similarly reported the safety and technical feasibility of the technique[43]. Chapman and Waxman[44] studied the propensity of CTCs as compared to sampling the PV under EUS guidance (19 gauge) with peripheral blood. In 18 patients, 100% sampling of CTC from the PV was achieved in comparison to 22.2% from the peripheral blood. Methodologically, the literature suggests multiple levels of consideration for PV sampling under EUS-guidance, due to limited data on safety and insubstantial unanimity of the technical feature of the procedure. Primarily, all bleeding risk should be addressed prior to the procedure and monitored anesthesia is an advocated preference in many studies. Secondarily, pre-assessing the PV under ultrasonography and FNA vein sampling was reviewed. The EUS-FNA needles available in today's market are the 19, 22, and 25 gauge sizes[44]. Chapman and Waxman[43], recommended the use of a 19-gauge FNA needle to allow adequate blood flow, that minimizes the time within the vessel to decreases clotting as compared to the smaller needles.

Ultimately, there is a lack of studies that assess the viability of the specimens obtained and the feasibility of the methodology. It is crucial to assess the patency of the vasculature with ultrasonographic doppler prior to the FNA access, in order to better reduce AEs.

Portal pressure gradient is an important measurement for the diagnosis of portal hypertension. Regardless of clinical evidence, a hepatic venous pressure gradient of 10 mmHg or more defines the presence of portal hypertension and is an important indicator of PH complication, most often for cirrhosis. Currently, a percutaneous approach exists for measuring PV pressure through a trans jugular access to the PV *via* the hepatic veins. Reduced conformity from patients due to catheterization makes an EUS-guided option more favorable[45].

Following the development of the compact manometer, EUS-guided portal pressure gradient measurement with a needle in the PV and manometer, accurately reflect an indicator of liver disease [27]. Under EUS, a 22-gauge FNA needle connected to a compact manometer, accurate hepatic venous pressure gradient measurement can be attained[46]. In a recent study by Hajifathalian *et al*[47], a simultaneous EUS-guided portosystemic pressure measurement and liver biopsy sampling in 24 patients with suspected liver disease or cirrhosis, was performed. Twenty-three patients reached technical success (96%) for portosystemic gradient measurement and 100% technical success for liver biopsy. The study concluded that EUS portosystemic gradient measurement and liver biopsy sampling provided a safe and feasible option in clinical practice. Table 3 lists studies on PV pressure gradient measurement, outlining technical success, features and complications, adapted from[48].

In the management of liver diseases, PV embolization (PVE) n is a possible intervention aimed at inducing atrophy of a lobe of the liver. This is advantageous, as it reduces the volume of the injured lobe prior to resection and concomitantly hypertrophies other healthy lobes, to decrease hepatic dysfunction and aiding preoperative preparations to liver lobectomy[27]. PVE is limited in multiple studies to animal models, due to the high-risk association with AEs, such as liver dysfunction. Loffroy *et al*[49] outlined PVE technique by accessing the portal system under EUS. Puncturing the peripheral branch by way of puncturing the left and embolizing the right branch is advantageous over puncturing and embolizing the right branch, due to easier catheterization. This method is conversely disadvantageous due to a high risk of damaging healthy liver remnants. Cirrhotic patients with portal pressure gradient larger than 12 mmHg, should avoid PVE due to detrimental AEs. Regarding the choice of the embolic agent, the authors suggested the use of a mixture of n-butyl-cyanoacrylate and iodized oil due to its rates of low morbidity. In anticipation to future advances, PVE under EUS-guidance can be appealing intervention in managing patients prior to surgical lobectomy.

Angiography

The direct access to the PV during an angiography may provide valuable clinical information. Unfortunately, routine practice avoids its implementation due to its invasive nature and high risk of complications[50]. A preliminary study in this field highlighted this fact in greater detail, as it showed that puncturing the PV with a 22-gauge needle led to high-risk bleeding measures in a porcine model[51]. In one study that evaluated the feasibility and safety of EUS-guided PV angiography with a smaller-caliber (25 gauge) FNA needle using carbon dioxide (CO_2) as a contrast agent in a porcine model. In 6 animal experimental trials, the authors achieved (19.83 ± 1.68 s) opacification of the entire portal system (visualization score 4.33 ± 0.52). The study reported no complications intraoperatively or at post-mortem examination, concluding that the study was feasible, safe, and technically simple. It is imperative to note that a major limitation to such studies is that they are acute animal models[52]. Replication into human disease remains confined in a plethora of possible complications and high bleeding risk.

Thrombus FNA

A large majority of patients suffering from hepatocellular carcinoma (HCC), have PV thrombosis. PV tumor thrombosis (PVTT) is essential as it is a poor prognostic sign and a contraindication for surgical hepatic resection. Extrahepatic PV access under EUS guidance, manages to access the thrombus without puncturing liver parenchyma, a favorable option for patients[27]. In 2015, Kayar *et al*[53] presented a case series of three cases that failed the normal route of imaging diagnosis of PV thrombus. Alternatively, from prior case reports, the patients were diagnosed with EUS-FNA of the PV thrombus as a first line diagnostic option. In all three cases presented, the authors used a 25-gauge FNA needle to biopsy the thrombus. Table 4 reports recent studies that highlighted cases of thrombus FNA-biopsy under EUS, notably when failed radiological diagnosis was unable to accurately stage HCC. Interestingly, Gimeno Garcia *et al*[54] in a multicentral study found that post EUS-FNA of thrombus, upstaging of HCC was prevalent up to 85.70%. In accordance with this finding, EUS-FNA biopsy of PVTT provides the most accurate staging diagnosis of HCC. High prospects for an EUS-guided intervention in diagnosing PVTT in patients that failed prior routes exist and should be studied in large RCT for a more widespread adaptation in everyday practice.

Drug administration

Even since the conception of curvilinear array echoendoscope in the 90's, the possibility to access structures with a needle under ultrasonographic visualization made treatment options to inaccessible

Table 3 Table summarizing technical features, success, and complications of studies on portal vein pressure gradient measurement

Ref.	Design	Technical success (%)	Adverse events	Post-procedural necropsy	Gauge needle used
Lai *et al*[51], 2004	Comparative Study - Animal Model	90	Subserosal hematoma in one porcine subject	After 4 d	22
Giday *et al*[52], 2007	Comparative Study - Animal Model	100	None	Day 0 and after 2 wk	19
Buscaglia *et al*[66], 2008	Comparative Study - Animal Model	100	None	Postprocedural	19
Huang *et al*[67], 2016	Comparative Study - Animal Model	100	None	Not reported	25
Schulman *et al*[68], 2016	Comparative Study - Animal Model	100	None	Postprocedural	25
Garg and Rustagi [48], 2017	Human Pilot Study	100	None	Not reported	25
Garg and Rustagi [48], 2017	Human Pilot Study	100	None	Occured on day 0, 1 and 7	25
Huang *et al*[69], 2017	Human Pilot Study	100	None	Not reported	25
Zhang *et al*[46], 2021	Prospective Study	91.70	None	Not reported	22

Table 4 Table summarizing studies and case reports of portal vein thrombus biopsy

Ref.	Design	Technical success (%)	Adverse events	Upstaging post EUS-FNA	Cytological analysis
Gimeno Garcia *et al* [54], 2018	Multicenter Study	87.50	None	85.70%	Used to determine final diagnosis
Rustagi *et al*[70], 2017	Prospective Study	100	None	37.50%	Malignant cytology in 12 patients out of 17 (70.6%; 10 positive, 2 suspicious)
Kayar *et al*[53], 2015	Case Report	100	None	Not reported	Invasion of PV by HCC
Moreno *et al*[71], 2014	Case Report	100	None	Not reported	Invasion of PV by HCC
Michael *et al*[72], 2011	Case Report	100	None	Not reported	Malignant cells consistent with poorly differentiated HCC

HCC: Hepatocellular carcinoma; EUS: Endoscopic ultrasound; PV: Portal vein; FNA: Fine needle aspiration.

structures possible. Further evolving into a therapeutic tool, being a minimally invasive approach for treating benign lesions, relieving compartmental pain, and controlling growth in unresectable malignancies is cutting edge[55]. EUS-guided therapeutic administration has been implemented apart from its varying levels of efficacy[56]. These ablative therapies under EUS-guidance are not a sole alternative to surgical resection, especially for metastatic tumors, but represent an option for patients that are not eligible for surgery. Moreover, recent studies show that chemotherapeutic administration into the PV increases the drug concentration in hepatic tissue than its systemic counterpart[57]. In 2016, an EUS-guided intervention for the injection of the PV was studied in a porcine model. Using a 22-gauge needle, 100mg of irinotecan, albumin-bound paclitaxel nanoparticles and doxorubicin loaded microbeads were injected into the PV. The study reported technical success in all animals, with no acute AEs occurring, suggesting a possible future avenue to be explored in human diseases[58].

CONCLUSION

Regrettably, to the best of our knowledge, EUS-guided treatment still has limitations and further studies are needed to demonstrate superiority over conventional medical and radiological therapies[18]. Primarily the steep learning curve and the need for expertise that may not be dispersed in all centers make it extremely difficult for guidelines to adapt strict recommendations in clinical practice[59]. Moreover, due to this revolutionary technology still being in the premature stages of adaptation into

clinical practice, a unified or standardized methodology doesn't exist. Whether the type of echo-endoscope, the positioning during therapy or the type of equipment used, a non-universal approach makes room for variable clinical outcomes and technical success rates[60]. On the other hand, EUS-guided therapy has potential to improve and become a main staple in the management of gastric varices [32]. In conclusion, EUS is without a doubt a novel diagnostic and therapeutic option for a variety of vascular complications, principally at the moment gastric variceal hemorrhage[59]. EUS offers a better understanding of the anatomic and hemodynamic components associated with the variceal system and offers advanced therapeutic options with sounder clinical outcomes. Although limited to major tertiary centers and operator dependence with a long learning curve, the adoption of EUS into clinical practice is plausible if EUS procedures were standardized, enhanced training tools for clinicians and better universal image interpretation methodology[26]. Artificial intelligence in aiding clinical technicians with image interpretation may be a captivating step in the right direction in the evolution of this vital technology.

FOOTNOTES

Author contributions: Fugazza A and Khalaf K conceived the design of the work, writing the article and acquiring data; Colombo M, Carrara S, Spadaccini M, Koleth G, Troncone E and Maselli R acquired data and prepared the figures; Repici A and Anderloni A revised it critically for important intellectual content; all authors reviewed and approved the final version of the paper.

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Erin Crawford, Ramy Sabe, Thomas J Sferra, Carolyn Apperson-Hansen, Ali S Khalili

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Abstract

BACKGROUND

Endoscopic procedures are becoming increasingly important for the diagnosis and treatment of gastrointestinal disorders during childhood, and have evolved from a more infrequent inpatient procedure in the operating room to a routine outpatient procedure conducted in multiple care settings. Demand for these procedures is rapidly increasing and thus there is a need to perform them in an efficient manner. However, there are little data comparing the efficiency of pediatric endoscopic procedures in diverse clinical environments. We hypothesized that there are significant differences in efficiency between settings.

AIM

To compare the efficiency and examine adverse effects of pediatric endoscopic procedures across three clinical settings.

METHODS

A retrospective chart review was conducted on 1623 cases of esophagogastroduodenoscopy (EGD) or combined EGD and colonoscopy performed between January 1, 2014 and May 31, 2018 by 6 experienced pediatric gastroenterologists in three different clinical settings, including a tertiary care hospital operating room, community hospital operating room, and free-standing pediatric ambulatory endoscopy center at a community hospital. The following strict guidelines were used to schedule patients at all three locations: age greater than 6 mo; American

Society of Anesthesiologists class 1 or 2; normal craniofacial anatomy; no anticipated therapeutic intervention (*e.g.*, foreign body retrieval, stricture dilation); and, no planned or anticipated hospitalization post-procedure. Data on demographics, times, admission rates, and adverse events were collected. Endoscopist time (elapsed time from the endoscopist entering the operating room or endoscopy suite to the next patient entering) and patient time (elapsed time from patient registration to that patient exiting the operating room or endoscopy suite) were calculated to assess efficiency.

RESULTS

In total, 58% of the cases were performed in the tertiary care operating room. The median age of patients was 12 years and the male-to-female ratio was nearly equal across all locations. Endoscopist time at the tertiary care operating room was 12 min longer compared to the community operating room (63.3 ± 21.5 min *vs* 51.4 ± 18.9 min, $P < 0.001$) and 7 min longer compared to the endoscopy center (*vs* 56.6 ± 19.3 min, $P < 0.001$). Patient time at the tertiary care operating room was 11 min longer compared to the community operating room (133.2 ± 39.9 min *vs* 122.3 ± 39.5 min, $P < 0.001$) and 9 min longer compared to the endoscopy center (*vs* 124.9 ± 37.9 min; $P < 0.001$). When comparing endoscopist and patient times for EGD and EGD/colonoscopies among the three locations, endoscopist, and patient times were again shorter in the community hospital and endoscopy center compared to the tertiary care operating room. Adverse events from procedures occurred in 0.1% ($n = 2$) of cases performed in the tertiary care operating room, with 2.2% ($n = 35$) of cases from all locations having required an unplanned admission after the endoscopy for management of a primary GI disorder.

CONCLUSION

Pediatric endoscopic procedures can be conducted more efficiently in select patients in a community operating room and endoscopy center compared to a tertiary care operating room.

Key Words: Pediatric endoscopy; Efficiency; Adverse events; Tertiary care operating room; Community operating room; Endoscopy center

Core Tip: This was a retrospective study where we compared the efficiency of pediatric endoscopic procedures in a tertiary care operating room, community operating room, and endoscopy center and secondarily examined adverse events of procedures across these settings. We found that with using strict, identical scheduling guidelines for all locations, undergoing esophagogastroduodenoscopy (EGD) or combined EGD and colonoscopy at the community hospital room and endoscopy center was significantly faster for the patient and endoscopist when compared to the tertiary care operating room. The rate of adverse events was similar across all three locations.

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INTRODUCTION

Endoscopic procedures are crucial for the diagnosis, treatment, and surveillance of gastrointestinal disorders in children. Moreover, the demand for these services is increasing[1]. Along with the increased utilization, the clinical setting in which these procedures are performed is changing and are now being performed as outpatient procedures conducted in multiple clinical settings[1-5]. While they are most commonly performed in operating rooms within tertiary care institutions or dedicated pediatric endoscopy suites, many endoscopies are being performed in outpatient centers[3].

With the overall increasing demand for endoscopic procedures, there is a need to perform them in an efficient manner. Locations outside of pediatric tertiary care centers have the potential to accommodate a high volume of patients due to the elimination of emergent procedures and scheduling of lower risk patients. Clinical reports regarding the development of adult and pediatric endoscopy units have focused on defining metrics used to assess efficiency, ranging from productivity metrics such as the number of procedures per hour to operational metrics such as turnover time[2,6]. Several adult studies

have shown turnover time, the time between procedures, varies among clinical settings (*e.g.*, hospitals, ambulatory surgery centers) and is the main factor contributing to delay of procedures and the primary predictor of the number performed per hour[7,8]. However, there are substantial differences in the workflow between pediatric and adult patients that limit the applicability of adult metrics to the pediatric population[9-11]. There is no universal consensus on how efficiency can be optimized in pediatrics and scant information on its application in outpatient endoscopy centers.

The main objective of our study was to evaluate the efficiency of endoscopic procedures performed by pediatric gastroenterologists in diverse clinical settings. Secondarily, we assessed adverse events associated with endoscopic procedures performed in select pediatric patients at non-tertiary care facilities.

MATERIALS AND METHODS

We conducted a retrospective chart review of patients cared for by the Division of Pediatric Gastroenterology, Hepatology & Nutrition at University Hospitals Rainbow Babies and Children's Hospital (Cleveland, OH, United States) who underwent an outpatient esophagogastroduodenoscopy (EGD) or combined EGD and colonoscopy between January 1, 2014 and May 31, 2018. This study was approved by the local institutional review board.

Locations

During the period of this study, the Division performed endoscopies at three locations, including pediatric tertiary care hospital operating room, community hospital operating room, and a free-standing pediatric ambulatory endoscopy center at a community hospital. All locations were staffed by the same pediatric anesthesia and endoscopy personnel. The tertiary care hospital had a single dedicated operating room for inpatient and outpatient procedures; the endoscopist did not perform endoscopies outside of the assigned operating room. The anesthesiologist assigned to the endoscopy cases in the tertiary care operating room potentially covered other surgical cases occurring simultaneously in other rooms. The community hospital operating room and the community pediatric ambulatory endoscopy unit consisted of one procedure room. The rooms in these latter two settings were dedicated to the outpatient endoscopic procedures; however, different from the tertiary care hospital, each room had a pediatric anesthesiologist assigned exclusively to that location. Endoscopic procedures were scheduled back-to-back: 60 min for combined EGD and colonoscopies at all locations; 60 min for EGD at the tertiary care operating room; and, 30 min for EGD at the community hospital and endoscopy center.

Endoscopic case characteristics

During the period of this study, our institution followed strict guidelines to schedule patients at the community locations. These guidelines were developed through consensus opinion among the pediatric gastroenterologists, pediatric anesthesiologists, and endoscopy personnel. Patients were eligible for these locations if the following criteria were met: age greater than 6 mo; American Society of Anesthesiologists class 1 (healthy person) or 2 (mild systemic disease); normal craniofacial anatomy; no anticipated therapeutic intervention (*e.g.*, foreign body retrieval, stricture dilation, control of bleeding, variceal ligation); and, no planned or anticipated hospitalization post-procedure. Additionally, urgent or emergent cases were not performed at these locations. For this analysis, we used the same criteria to select patients undergoing endoscopy at the tertiary care hospital operating room for comparison. Also, the last case of each day was excluded from analysis as we are unable to calculate the endoscopist time. Cases that preceded inpatient procedures at the tertiary care operating room also were excluded to ensure timing and scheduling of cases were as similar as possible at all three locations.

Physicians

We reviewed only those cases performed by the pediatric gastroenterologists who performed endoscopies at the tertiary care operating room and one of the other locations. These 6 pediatric gastroenterologists were board certified, experienced endoscopists.

Data collection

We extracted data for all endoscopic procedures meeting the above criteria. Fewer cases were performed at the community ambulatory endoscopy center as compared to the other locations. To control for this disparity, cases performed at that site were matched by physician with cases performed at the tertiary care operating room; the cases from the tertiary care operating room were selected chronologically at the start of a calendar year until the number of cases between the two locations were approximately equal for each of those three physicians. Patient demographics, time variables (patient registration, patient and physician entering operating room, and patient exiting operating room), procedural or anesthesia complications, unexpected admissions, and fellow participation in the procedure were extracted from the medical record.

Adverse events were defined as endoscopic complications (*e.g.*, gastrointestinal bleeding or perforation), sedation and cardiopulmonary complications (*e.g.*, respiratory failure, need for intubation), any cause necessitating unintended emergency department visit or hospital admission, and hospital admission for ongoing medical care. We included hospital admission for ongoing medical care as an adverse event as patients undergoing endoscopy in the community settings would require transportation to the tertiary care hospital for care (also see guidelines for scheduling above).

Endoscopist time (ET) and patient time (PT) were calculated for each case. ET was defined as elapsed time from the endoscopist entering the operating room or endoscopy suite to the next patient entering. PT was defined as elapsed time from patient registration to that patient exiting the operating room or endoscopy suite. These times by definition include room turnover time and provide estimates of real time for the physician and patient.

Statistical analyses

Statistical analyses were performed by a trained statistician. Descriptive statistics were generated for each of the variables collected. Categorical data are reported as frequencies and percentages and when appropriate, χ^2 analyses were used. Continuous data are reported as numbers (n), means and standard deviations, and medians, and when appropriate, analysis of variance and unpaired t-test were used for analyses. Unless otherwise stated, statistical testing was conducted using two-sided alternatives with a type I error level of 0.05. SAS version 9.4 (SAS Institute Inc., Cary, NC, United States) was used to generate the statistics.

RESULTS

We identified 1623 cases (Table 1). Just over half were performed in the tertiary care operating room. The fewest were performed in the community ambulatory endoscopy center (7.6%). All cases were performed under monitored anesthesia care using propofol. The median age of the patients was 12 years, and the male-to-female ratio was nearly equal. There were no differences in age or sex among the cases performed at each endoscopy site or by each physician. Fellows participated in 38% of cases, with the highest percentage in the tertiary care operating room.

Efficiency

We found the tertiary hospital operating room to be the least efficient site to perform endoscopy even controlling for physician, patient age, fellow participation, and type of procedure (Table 2). The ET in the tertiary hospital operating room was 11.9 min longer than in the community operating room ($P < 0.001$) and 6.7 min longer than in the community endoscopy center ($P < 0.001$). Likewise, the PT at the tertiary care operating room was 11.2 min longer than the community operating room ($P < 0.001$) and 8.3 min longer than the endoscopy center ($P < 0.001$).

We compared the ET and PT for EGD and EGD/colonoscopies between the specific locations given that differences in case mix amongst locations may have affected the results, and confirmed the community operating room and endoscopy center were more efficient for each of these types of procedures (Table 3). We further evaluated the times based on individual physicians. Compared to the times in the tertiary care operating room, all of the physicians had a shorter ET in the community operating room and endoscopy center, and 5 of the 6 physicians had a shorter PT in the community operating room and endoscopy center compared to the tertiary care operating room (Table 4). The 1 physician (physician 6 in Table 4) with the longer PT in the community operating room compared to the tertiary care operating room (136.5 ± 35.7 *vs* 135.9 ± 41.8), also had the longest patient and endoscopist times overall. We did not calculate the statistical significance of ET and PT between physicians because the proportions of cases across locations were not equal.

Using analysis of variance, fellow participation did not significantly affect endoscopist or patient time when considering all cases, and we found that location accounted for the affect ($P < 0.001$). Fellow participation in the tertiary care operating room was associated with longer PT and ET, and the presence of a fellow overall resulted in the longest times.

Adverse events

Unplanned admissions following an endoscopic procedure occurred for a small number of patients (all locations, 2.2%, $n = 35$). The majority of these ($n = 33$) were for further management of a primary GI disease (*e.g.*, inflammatory bowel disease) and not an endoscopic or anesthesia related complication. Patients were less frequently admitted for any reason from each of the two community-based locations as compared to the tertiary operating room (community operating room, 0.2% of total at site, $n = 4$; community endoscopy center 0.1% of total at site, $n = 1$; tertiary hospital operating room, 1.8% of total at site, $n = 30$). Endoscopic complications occurred in two of the evaluated cases (0.1%). Both involved patients undergoing an EGD and colonoscopy in the tertiary hospital operating room. One patient was admitted to the pediatric intensive care unit for management of gastrointestinal bleeding requiring a blood transfusion and the other to the general medical unit for observation for concern of a

Table 1 Demographics, procedures, and fellow participation by location

Characteristic	Value			
	Tertiary care OR	Community OR	Endoscopy center	Overall
Age, yr (median)[1]	11	12	12	12
Male, *n* (%)[1]	494 (52.4)	268 (48.0)	63 (51.2)	825 (50.8)
EGD, *n* (%)	537 (57)	283 (50.7)	56 (45.5)	876 (54)
EGD/colonoscopy, *n* (%)	405 (43)	275 (49.3)	67 (54.4)	747 (46)
Total procedures, *n* (%)	942 (100)	558 (100)	123 (100)	1623 (100)
Fellow participation, *n* (%)	499 (53)	89 (16)	25 (20)	613 (38)

[1]There were no significant differences in the distribution of age and sex across the clinical settings. EGD: Esophagogastroduodenoscopy; OR: Operating room.

Table 2 Endoscopist time and patient time in minutes by location

	Tertiary care OR	Community OR	Endoscopy center	*P* value[1]
ET (mean ± SD)	63.3 ± 21.5	51.4 ± 18.9	56.6 ± 19.3	< 0.001
PT (mean ± SD)	133.2 ± 39.9	122.0 ± 39.5	124.9 ± 37.9	< 0.001

[1]ANOVA controlling for physician, patient age, fellow participation, and type of procedures. ET: Endoscopist time; OR: Operating room; PT: Patient time; SD: Standard deviation.

Table 3 Endoscopist time and patient time in minutes by location and procedure

	Procedure	Tertiary care OR	Community OR	Endoscopy center	*P* value
ET (mean ± SD)	EGD	63.2 ± 20.2	39.6 ± 13.6	45.0 ± 13.3	< 0.001
	EGD/colonoscopy	75.6 ± 17.3	63.4 ± 16.0	66.3 ± 18.0	< 0.001
PT (mean ± SD)	EGD	121.4 ± 39.0	107.7 ± 34.2	112.9 ± 31.8	< 0.001
	EGD/colonoscopy	148.4 ± 36.1	137.4 ± 38.9	135.0 ± 39.5	< 0.001

ET: Endoscopist time; OR: Operating room; PT: Patient time; SD: Standard deviation.

gastrointestinal bleed. A fellow was present during the endoscopy for one of the two complications.

DISCUSSION

The goals of our study were to assess the efficiency of pediatric endoscopic procedures in different clinical settings and to evaluate whether the performance of these procedures in a community setting was associated with an excess of adverse events. Changing indications for endoscopic procedures and a steady increase in gastrointestinal disease burden in this population resulted in an increase in demand for these procedures to which the medical community must adapt[1]. From 2011 to 2018, our institution expanded from three to nine pediatric gastroenterologists and the number of completed endoscopic procedures more than doubled. Improving efficiency without compromising safety is essential to accommodate the increased demand of endoscopic procedures and prevent delays in diagnosis and treatment.

We found it was more efficient to perform endoscopic procedures in two community-based locations compared to a tertiary care operating room. As our measures of efficiency, we used ET to measure time between cases for the endoscopist including room turn-over and other system delays and PT to include time spent at the hospital or endoscopy unit except for the time post-endoscopy in recovery. The ET was 6.7 to 11.9 min and the PT was 8.3 min to 11.2 min shorter in the endoscopy center and community operating room, respectively compared to the tertiary care operating room. The differences in ET and PT are likely due to factors specific to the tertiary care location rather than type or complexity of the case

Table 4 Endoscopist time and patient time in min by physician

Physician	Endoscopist time			Patient time		
	Tertiary care OR	Community OR	Endoscopy center	Tertiary care OR	Community OR	Endoscopy center
1	61.9 ± 23.1	53.2 ± 20.2		131.1 ± 38.3	126.7 ± 44.9	
2	63.9 ± 17.4	45.5 ± 14.5		142.9 ± 38.9	120.8 ± 34.9	
3	63.4 ± 22.4	45.5 ± 14.5		128.3 ± 42.4	110.2 ± 31.1	
4	64.4 ± 19.1		47.8 ± 13.5	126.0 ± 36.7		113.6 ± 38.4
5	63.4 ± 16.9		59.3 ± 19.5	160.8 ± 28.8		128.0 ± 33.7
6	68.6 ± 22.5		65.4 ± 20.7	135.9 ± 41.8		136.5 ± 35.7

Data are presented as mean ± SD. OR: Operating room.

as we controlled for these variables. If we did not employ the same criteria used to schedule patients in the community locations to select the comparator patients at the tertiary care operating room, the times in the tertiary care operating room would be longer as emergent and complex cases (*e.g.*, variceal banding, multiple comorbidities) would be included and likely result in delays.

Several studies have described factors that can impact efficiency of endoscopic procedures[7,8,12,13]. These may be related to the patient (*e.g.*, late to registration or no-show), physician (*e.g.*, late to procedure), or support personnel (*e.g.*, room turnover time). While we did not directly determine causes of the differences in efficacy besides fellow participation, our results support previous findings that decreases in efficiency at the tertiary care center are less likely to be solely related to patient or endoscopist behavior as ET and PT were almost always individually faster at the community locations. However, the endoscopist's efficiency may become a limiting factor after a certain point. For example, physician 6 had comparatively longer ET and PT times at the tertiary care center and at the endoscopy center and these were the longest times overall. This may explain why the community OR had lower ET and PT times compared to the endoscopy center, although both community locations were still more efficient when compared to the tertiary care center. Overall, the loss in efficiency may be a system problem, where possible location specific factors include room turnover, availability of anesthesiology staff, or endoscopist delayed with other tasks. Trainee participation has been shown to adversely impact efficiency by prolonging procedures[8]. In our study, while fellow participation did not affect efficiency when considering all cases included, their participation specifically in the tertiary care operating room was associated with longer ET and PT. This might be due to our institution's practice of only having senior fellows participate in endoscopy sessions at the community sites. First year fellows participate in endoscopies at the tertiary care operating room.

Regarding anesthesiologist participation during endoscopic procedures, they are often being shared with other operating rooms at the tertiary care center, which may delay procedural start time. Having a dedicated anesthesiologist at the community locations eliminates this problem. It is important to note, monitored anesthesia care with propofol was used in all of the patients in this study and has been shown to be safe and efficient due to its rapid sedation and recovery time[14,15]. Thus, our data may not translate to centers using agents other than propofol or have non-anesthesiologist staff perform sedation.

Practically, the accumulated saved time at the community locations on a typical 8-h day could reach 90 min allowing for at least two additional cases per day. Adjustments to scheduling and allotted time for procedures may help meet the increasing demand by allowing more procedures to be performed in a day. Other direct benefits from performing endoscopic procedures more efficiently are increases in patient satisfaction and institutional revenue. Performing a given number of procedures within a shorter time period will directly impact the physician's ability to complete other tasks.

We evaluated adverse events defined as endoscopic complications, anesthesia and respiratory complications, and unintended admissions occurring within 72 h of the procedure. We did not evaluate mild adverse events (*i.e.*, nausea, throat pain). There were no procedural, anesthesia and respiratory complications at the community hospital and the ambulatory endoscopy center. Although there were fewer adverse events within the community locations, the number of cases included in this study is too low to determine whether endoscopies in these locations are safer than in a tertiary care facility[16-18]. To make this determination, a large multi-institutional study performed over several years is required. Thus, we only described our experience.

The major strengths of our study were the ability to compare cases performed by each endoscopist between two different locations as well as to compare the ET and PT among all 6 physicians at all three locations. Endoscopic procedures were performed in three clearly delineated locations with the same support staff and the use of strict criteria for scheduling of patients within the community centers. This study due to its retrospective nature has few weaknesses. All cases performed in the tertiary operating

room were not used in the analysis to allow us to match the relatively smaller number of cases at the community sites. However, given that the cases were all conducted within a similar time period and the physicians were all experienced endoscopists, the excluded cases are unlikely to reflect a bias in the results. There was a difference in the allotted time for EGD between the tertiary care operating room and community locations, however we do not believe this had an impact on the study as the procedures were scheduled one after the other with the guidance to perform the subsequent procedure once the operating room was available. Also, the study is underpowered to detect true differences in the rates of adverse events.

CONCLUSION

In conclusion, we found that in select pediatric patient populations, endoscopic procedures can be performed more efficiently in non-tertiary care centers. These data may help future guidelines on building efficient outpatient pediatric endoscopy suites. Further investigation is needed to understand why these procedures are more efficient at community locations. Also, our data forms a foundation upon which further studies can be performed to evaluate whether there is an increased risk to the patient with this practice. Being able to provide more efficient care in a convenient location for selected patients can increase satisfaction while accommodating the increase need for such procedures.

ARTICLE HIGHLIGHTS

Research background

There has been an increase in pediatric endoscopic procedures over time and an increased demand to perform them efficiently. These procedures are now being performed in more diverse clinical settings, from tertiary care operating rooms to ambulatory centers. Data is lacking with regards to safety and efficiency of these procedures across multiple clinical settings which is needed information as the pediatric endoscopic landscape diversifies.

Research motivation

We aimed to understand efficiency and adverse rate events of pediatric endoscopic procedures across multiple clinical settings as there is a paucity of this data in the literature. This research could help lay the foundation for guidelines of building outpatient pediatric endoscopy suites or ambulatory centers.

Research objectives

The main objective of our study was to evaluate the efficiency of endoscopic procedures performed by pediatric gastroenterologists in diverse clinical settings, particularly ambulatory centers as compared to a tertiary care operating room. We also assessed adverse events associated with endoscopic procedures performed across these clinical settings.

Research methods

A retrospective chart review was conducted of esophagogastroduodenoscopy (EGD) or combined EGD and colonoscopies performed over a 4 year period by 6 experienced gastroenterologists in three settings; a tertiary care hospital operating room, community hospital operating room, and a free-standing pediatric ambulatory endoscopy center at a community hospital. Demographics, times, admission rates and adverse events were collected and efficiency was measured in endoscopist time (elapsed time from the endoscopist entering the operating room or endoscopy suite to the next patient entering) and patient time (elapsed time from patient registration to that patient exiting the operating room or endoscopy suite). Statistical analyses were performed by a trained statistician and descriptive statistics were generated for each of the variables collected.

Research results

The majority of the cases were performed at the tertiary care operating room. Endoscopist time at the tertiary care operating room was 12 min longer compared to the community operating room (63.3 ± 21.5 min *vs* 51.4 ± 18.9 min; $P < 0.001$) and 7 min longer compared to the endoscopy center (*vs* 56.6 ± 19.3 min; $P < 0.001$). Patient time at the tertiary care operating room was 11 min longer compared to the community operating room (133.2 ± 39.9 min *vs* 122.3 ± 39.5 min; $P < 0.001$) and 9 min longer compared to the endoscopy center (*vs* 124.9 ± 37.9 min, $P < 0.001$). Adverse events occurred in 0.1% of cases performed in the tertiary care operating room.

Research conclusions

We found that it was more efficient to perform EGD and colonoscopies at a community hospital

operating room and a free-standing pediatric ambulatory endoscopy center at a community hospital when compared to a tertiary care operating room in a select pediatric population. There was not an increased adverse event rate that we observed at these satellite locations when compared to the tertiary care operating room. Being able to perform these procedures safely and efficiently in multiple clinical settings may help meet the growing demand of endoscopic procedures in children.

Research perspectives

This research showed that pediatric endoscopic procedures are efficient in multiple clinical settings in a select pediatric population. Larger, prospective studies are needed to validate what we have found and to better assess safety. Our research could help lay the foundation for future guidelines on building efficient outpatient pediatric endoscopy suites.

FOOTNOTES

Author contributions: Crawford E, Sabe R, Sferra TJ, Apperson-Hansen C, and Khalili AS contributed equally to this work; Crawford E, Sabe R, Sferra TJ, Apperson-Hansen C, and Khalili AS designed the research study; Crawford E and Khalili AS performed the research; Crawford E and Apperson-Hansen C analyzed the data; Crawford E, Sabe R, Sferra TJ, Apperson-Hansen C, and Khalili AS wrote the manuscript; all authors have read and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of the University Hospitals (No. CR00002806).

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Retrospective Study

Endoscopic ultrasound diagnostic gain over computed tomography and magnetic resonance cholang-iopancreatography in defining etiology of idiopathic acute pancreatitis

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Abstract

BACKGROUND

About 10%-30% of acute pancreatitis remain idiopathic (IAP) even after clinical and imaging tests, including abdominal ultrasound (US), contrast-enhanced computed tomography (CECT) and magnetic resonance cholangiopancreatography (MRCP). This is a relevant issue, as up to 20% of patients with IAP have recurrent episodes and 26% of them develop chronic pancreatitis. Few data are available on the role of EUS in clarifying the etiology of IAP after failure of one or more cross-sectional techniques.

AIM

To evaluate the diagnostic gain after failure of one or more previous cross-sectional exams.

METHODS

We retrospectively collected data about consecutive patients with AP and at least one negative test between US, CECT and MRCP, who underwent linear EUS between January 2017 and December 2020. We investigated the EUS diagnostic yield and the EUS diagnostic gain over different combinations of these cross-

sectional imaging techniques for the etiologic diagnosis of AP. Types and frequency of EUS diagnosis were also analyzed, and EUS diagnosis was compared with the clinical parameters. After EUS, patients were followed-up for a median of 31.5 mo to detect cases of pancreatitis recurrence.

RESULTS

We enrolled 81 patients (63% males, mean age 61 ± 18, 23% with previous cholecystectomy, 17% with recurrent pancreatitis). Overall EUS diagnostic yield for AP etiological diagnosis was 79% (20% lithiasis, 31% acute on chronic pancreatitis, 14% pancreatic solid or cystic lesions, 5% pancreas divisum, 5% autoimmune pancreatitis, 5% ductal abnormalities), while 21% remained idiopathic. US, CECT and MRCP, taken alone or in combination, led to AP etiological diagnosis in 16 (20%) patients; among the remaining 65 patients, 49 (75%) obtained a diagnosis at EUS, with an overall EUS diagnostic gain of 61%. Sixty-eight patients had negative US; among them, EUS allowed etiological diagnosis in 59 (87%). Sixty-three patients had a negative CECT; among them, 47 (74%) obtained diagnosis with EUS. Twenty-four had a negative MRCP; among them, 20 (83%) had EUS diagnosis. Twenty-one had negative CT + MRCP, of which 17 (81%) had EUS diagnosis, with a EUS diagnostic gain of 63%. Patients with biliary etiology and without previous cholecystectomy had higher median values of alanine aminotransferase (154 *vs* 25, $P = 0.010$), aspartate aminotransferase (95 *vs* 29, $P = 0.018$), direct bilirubin (1.2 *vs* 0.6, $P = 0.015$), gamma-glutamyl transpeptidase (180 *vs* 48, $P = 0.006$) and alkaline phosphatase (150 *vs* 72, $P = 0.015$) Chronic pancreatitis diagnosis was more frequent in patients with recurrent pancreatitis at baseline (82% *vs* 21%, $P < 0.001$). During the follow-up, AP recurred in 3 patients, one of which remained idiopathic.

CONCLUSION

EUS is a good test to define AP etiology. It showed a 63% diagnostic gain over CECT + MRCP. In suitable patients, EUS should always be performed in cases of IAP. Further prospective studies are needed.

Key Words: Endoscopic ultrasound; Idiopathic acute pancreatitis; Diagnostic gain; Computed tomography; Magnetic resonance cholangiopancreatography

Core Tip: Acute pancreatitis (AP) is a common and potentially severe disease. Imaging techniques allow an etiological diagnosis in most cases. However, about 20% of cases remain idiopathic, with negative consequences on patients' outcomes. Endoscopic ultrasound (EUS) has emerged as a valid technique for the assessment of AP etiology. We share our experience with EUS in the identification of idiopathic AP etiology, after failure of one or more cross-sectional imaging techniques. We found a superiority of EUS over the standard cross-sectional imaging techniques. We therefore suggest the use of EUS to define idiopathic AP etiology in all suitable patients.

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INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disorder characterized by the abnormal activation of digestive enzymes within the pancreatic gland. AP leads to the acute injury of the pancreas and may involve remote organs and systems. AP is one of the most common causes of hospitalization in the United States and Europe[1]. In most cases (about 80%), the prognosis is rapidly favorable[2]. Nevertheless, acute necrotizing pancreatitis may develop in up to 20% of cases, and it is associated with significant rates of early organ failure (38%), need for intervention (38%) and death (15%)[3].

The most common AP etiologies are common bile duct stones and alcohol abuse, accounting for about 60%-70% of all the cases[4]. Other etiologies include functional or anatomic lesions (pancreas divisum, pancreatic duct strictures/tumors, ampullary stenosis or sphincter of Oddi dysfunction), drugs, metabolic causes (hypertriglyceridemia, hypercalcemia), autoimmune disease, mechanical injury (*e.g.*, blunt abdominal trauma, postoperative), infections, ischemia, hereditary conditions and toxins[5].

AP etiology can be found in most cases by combining cross-sectional abdominal imaging techniques, such as ultrasound (US), contrast-enhanced computed tomography (CECT) and magnetic resonance cholangiopancreatography (MRCP). However, 10%-30% of AP remains idiopathic (IAP) after clinical, laboratory and imaging tests[6,7]. This is a relevant issue, as 20% of patients with IAP have recurrent episodes, and 20%-30% of them develop chronic pancreatitis[6]. In recent years, endoscopic US (EUS) has emerged as a useful tool for the etiological diagnosis of AP. A recent systematic review and meta-analysis demonstrated that EUS is able to identify a potential etiology in the majority of patients with IAP[8].

EUS has shown high diagnostic accuracy for the identification of microlithiasis missed at CECT scan or MRCP[9,10]. Moreover, in a smaller but relevant percentage of cases, EUS detected small pancreatic or ampullary lesions that were not identified at CECT or magnetic resonance imaging[11-13]. To date, few data are available about the role of EUS after failure of multiple cross-sectional imaging techniques and specifically evaluating the diagnostic gain of EUS in this setting. The present study aimed to evaluate the role of EUS in the assessment of IAP etiology when US, CECT and MRCP failed.

MATERIALS AND METHODS

Study population and data collection

We performed a retrospective, single-center study. We analyzed a database of consecutive adult patients prospectively enrolled between January 2017 and December 2020 to the Ospedale Maggiore of Cremona with a diagnosis of AP. The diagnosis of AP was made when 2 of 3 of the following criteria were met: abdominal pain consistent with pancreatitis; increased serum amylase or lipase levels, by at least 3 times the upper normal of limit; and characteristic findings on conventional radiologic methods (transabdominal US and/or CECT scan). MRCP was performed as a second-line technique after a negative US and/or CECT.

A thorough medical history and complete blood tests were collected for each patient at the clinical presentation. For final inclusion in the study analyses, the following criteria were ruled out: (1) History of alcohol or other toxic substance abuse; (2) Recent abdominal trauma; (3) Medications potentially related to AP; (4) Metabolic disorder like hypertriglyceridemia (≥ 1000 mg/dL) or hypercalcemia; (5) Clear etiology of AP identified at US, CECT or MRCP, without the need for further investigations; and (6) In the case of recurrent pancreatitis (*i.e.* ≥ 2 episodes of AP), a genetic cause was ruled out by testing for *CFTR*, *SPINK-1* and *PRSS1* mutations.

Therefore, the patients included in final analysis were those diagnosed with idiopathic acute pancreatitis (IAP), according to the American College of Gastroenterology guidelines[14].

All patients included in the study had undergone EUS after at least one US, CECT or MRCP test. Specifically, EUS was performed after a negative cross-sectional technique to investigate the AP etiology and after a positive exam to confirm a suspected diagnosis, to better characterize a lesion or to obtain biopsies.

After EUS examination, patients were followed up for at least 12 mo (median 31.5 mo, range 12-55), and recurrent episodes of acute pancreatitis were recorded.

The primary aim of the study was to evaluate the diagnostic gain of EUS in the identification of IAP etiology after failure of one or more previous cross-sectional exams. The secondary aims were: to assess the overall EUS diagnostic yield for IAP etiology; to compare the baseline clinical features with the IAP diagnosis; and to analyze the frequency and types of AP recurrence during the follow-up.

Endoscopic ultrasound

EUS examination was performed by 2 experienced operators (≥ 250 exams per year) using a linear echoendoscope (Pentax Medical EG3870UTK and EG38-J10UT), after informed consent had been obtained, with the patient in a left-side position under conscious sedation. EUS was mainly performed during admission after the acute phase of pancreatitis was clinically resolved, unless conditions such as persistent biliary obstruction required earlier evaluation. EUS was performed as an outpatient procedure in cases of mild pancreatitis with early patient discharge.

The examination was considered diagnostic with the following findings: biliary stones, criteria for chronic pancreatitis, presence of solid or cystic pancreatic lesions, pancreatobiliary duct abnormality, pancreas divisum, and features of autoimmune pancreatitis.

In detail: (1) Biliary etiology was diagnosed if stones or microlithiasis/biliary sludge were seen inside the gallbladder or the common bile duct. Biliary stones were defined as hyperechoic structures with an acoustic shadow, microlithiasis was defined as hyperechoic structures of 3 mm or less in diameter, and biliary sludge was defined as a hyperechoic material without an acoustic shadow[15]; (2) Chronic

pancreatitis was defined according to the Rosemont criteria[16]; (3) Duct abnormality was diagnosed if a long pancreatobiliary junction (> 15 mm) was identified[17]; (4) Pancreas divisum was described in the presence of a dominant dorsal duct with or without evidence of communication between the ventral and dorsal ducts, or if the main pancreatic duct could not be traced from the major papilla[18]; (5) Solid or cystic pancreatic lesions were considered as the cause of AP if obstruction of the pancreatic duct was seen at EUS examination; and (6) The diagnosis of autoimmune pancreatitis was made when parenchymal or ductal features were seen (*e.g.*, diffuse pancreas enlargement with delayed enhancement), and the International Consensus Diagnostic Criteria were met[19].

Statistical analysis

The categorical variables were described as absolute frequency and percentage. The continuous variables with normal distribution were described as mean ± SD, whereas the continuous variables without normal distribution were given as median and range. Mann-Whitney test and ^{2} or Fisher's exact tests were used to associate baseline clinical and biochemical variables with biliary pancreatitis. Diagnostic yield of EUS was calculated as the overall percentage of etiological diagnosis obtained through EUS examination. EUS diagnostic gain was calculated as the percentage of additional diagnoses obtained at EUS over the total number of patients undergoing US, CECT and/or MRCP. All the analyses were carried out by computer software IBM SPSS Statistics (release 25; IBM Corporation, United States).

RESULTS

Between March 2017 and December 2020, a total of 81 patients underwent EUS for IAP (38% female, mean age at enrollment 61 ± 18 years). Fifteen (23%) patients had previous cholecystectomy, whereas 49 (77%) had an intact gallbladder. First episode of AP was the indication of EUS in 52 (81%) patients, while 12 (19%) patients had recurrent pancreatitis (58% with one episode, 42% with 2 or more episodes). The median time interval between patient admission and EUS was 5 d (range, 2-27). All patients' demographic and clinical characteristics are summarized in Table 1.

Diagnostic yield of EUS and types of diagnosis

Overall, EUS led to an etiological diagnosis in 64 (79%) of the 81 patients. The diagnoses were as follows: 16 gallstone diseases, 25 acute on chronic pancreatitis, 4 pancreas divisum, 4 pancreatic duct anomalies, 11 solid or cystic lesions (4 pancreatic carcinomas with a maximum diameter of 15, 18, 20 and 24 mm; 2 ampullary adenomas of 8 and 13 mm; 5 branch-duct intraductal papillary mucinous neoplasms with high-risk stigmata or worrisome features) and 4 with criteria of autoimmune conditions. Example images of the main diagnosis obtained by EUS are shown in Figure 1. All patients underwent EUS and at least one exam with US, CECT and MRCP. The three cross-sectional techniques, alone or in combination, led to AP etiological diagnosis in 16 (20%) of the 81 patients. All diagnoses were confirmed at the following EUS. Among the remaining 65 patients, 49 (75%) obtained a diagnosis at EUS, with an overall EUS diagnostic gain of 61%.

US and EUS: Seventy-two (89%) patients underwent US, which allowed an etiological diagnosis in 4 (6%) cases. Among the 68 patients with a negative US, EUS allowed an etiological diagnosis in 59 (87%): 14 biliary pancreatitis, 25 acute on chronic pancreatitis, 2 pancreas divisum, 4 pancreatic duct anomalies, 10 solid or cystic lesions and 4 autoimmune conditions.

CECT and EUS: CECT scan was performed in 72 patients (89%), 9 of which (13%) resulted with an etiological diagnosis. Forty-seven (74%) out of the 63 patients with negative CECT obtained an etiological diagnosis at EUS: 10 lithiasis, 18 acute on chronic, 4 pancreas divisum, 4 duct anomalies, 9 solid/cystic lesions and 2 autoimmune pancreatitis.

MRCP and EUS: MRCP was performed in 32 patients, among which 8 (24%) obtained an etiological diagnosis. EUS allowed a diagnosis in 20 (83%) of the 24 patients with negative MRCP: 4 biliary etiology, 9 acute on chronic pancreatitis, 1 pancreas divisum, 1 pancreatic duct anomaly, 4 solid or cystic lesions and 1 autoimmune pancreatitis.

Diagnostic gain of EUS in cases of previous negative exams

US + CECT: A combination of US and CECT was performed in 63 patients (78%); of the 54 patients with missed diagnosis at both US and CECT, 45 (83%) received a diagnosis at EUS: 10 biliary etiology, 17 acute on chronic pancreatitis, 3 pancreas divisum, 4 pancreatic duct anomalies, 8 solid or cystic lesions and 3 autoimmune conditions. EUS diagnostic gain over US + CECT was 71%.

US + MRCP: A combination of US and MRCP was performed in 31 patients (38%); of the 23 US + MRCP missed diagnosis, 20 (87%) were identified at EUS: 4 biliary etiology, 9 acute flares on chronic pancreatitis, 1 pancreas divisum, 1 pancreatic duct anomalies, 4 solid or cystic lesions and 1 inflammatory-

Table 1 Demographic and clinical features of the 64 patients analyzed

Parameter	*n* = 81	EUS diagnosis, *n* = 64	Missed EUS diagnosis, *n* = 17	*P* value
Male, *n* (%)	51 (63)	43 (67)	8 (46)	0.208
Age at enrollment, mean ± SD, yr	61 ± 18	62 ± 18	59 ± 16	
Previous cholecystectomy, *n* (%)	19 (23)	18 (28)	0	0.028
Recurrent pancreatitis, *n* (%)	14 (17)	14 (22)	0	0.101
One episode, *n* (%)	7 (9)			
≥ 2 episodes, *n* (%)	6 (7)			
Amylase, median (range)	468 (107-4988)	465 (123-4988)	500 (107-4753)	0.861
Lipase, median (range)	777 (87-23840)	774 (87-23840)	780 (96-12800)	0.914
Gamma-glutamyl transpeptidase, median (range)	70 (9-1665)	70 (9-1665)	125 (11-640)	0.707
Alkaline phosphatase, median (range)	78 (32877)	78 (32-877)	90 (32-185)	0.707
Direct bilirubin, median (range)	0.7 (0.2-8.5)	0.4 (0.2-3)	0.7 (0.2-8.5)	0.933
Alanine aminotransferase, median (range)	34 (6-793)	34 (6-793)	33 (7-596)	0.488
Aspartate aminotransferase, median (range)	38 (11-704)	34 (11-704)	33 (15-301)	0.732
Abdominal US, *n* (%)	72 (89)	63 (98)	9 (54)	< 0.001
Abdominal CECT, *n* (%)	72 (89)	56 (88)	16 (94)	1.000
MRCP, *n* (%)	32 (39)	28 (44)	4 (24)	0.220
EUS findings, *n* (%)		NA	NA	NA
Normal (final IAP diagnosis)	17 (21)			
Biliary	16 (20)			
Microlithiasis / biliary sludge	9 (11)			
Acute on chronic pancreatitis	25 (31)			
Solid or cystic lesions	11 (14)			
Pancreatic adenocarcinoma	4 (5)			
Ampullary adenoma	2 (3)			
BD-IPMN with high-risk stigmata or worrisome features	5 (6)			
Pancreas divisum	4 (5)			
Ductal anomaly	4 (5)			
Autoimmune criteria	4 (5)			

BD-IPMN: Branch-duct intraductal papillary mucinous neoplasms; CECT: Contrast enhanced computed tomography; IAP: Idiopathic acute pancreatitis; MRCP: Magnetic resonance cholangiopancreatography; SD: Standard deviation; US: Ultrasound; EUS: Endoscopic ultrasound; NA: Not available.

autoimmune condition. EUS diagnostic gain over US + MRCP was 65%.

CECT + MRCP: CECT and MRCP were both performed in 27 patients; of the 21 CECT + MRCP missed diagnoses, 17 (81%) were identified at EUS: 3 gallstone disease, 7 acute on chronic pancreatitis, 1 pancreas divisum, 1 pancreatic duct anomalies, 4 solid or cystic lesions and 1 autoimmune condition. EUS diagnostic gain over CECT + MRCP was 63%.

US + CECT + MRCP: Finally, 25 patients (31%) received all 3 cross-sectional techniques, without obtaining the AP etiological diagnosis in 19 cases; among them, EUS allowed a diagnosis in 17 (89%) cases: 3 gallstone disease, 7 acute on chronic pancreatitis, 1 pancreas divisum, 1 pancreatic duct anomalies, 4 solid or cystic lesions and 1 autoimmune condition. EUS diagnostic gain over US + CECT + MRCP was 68%.

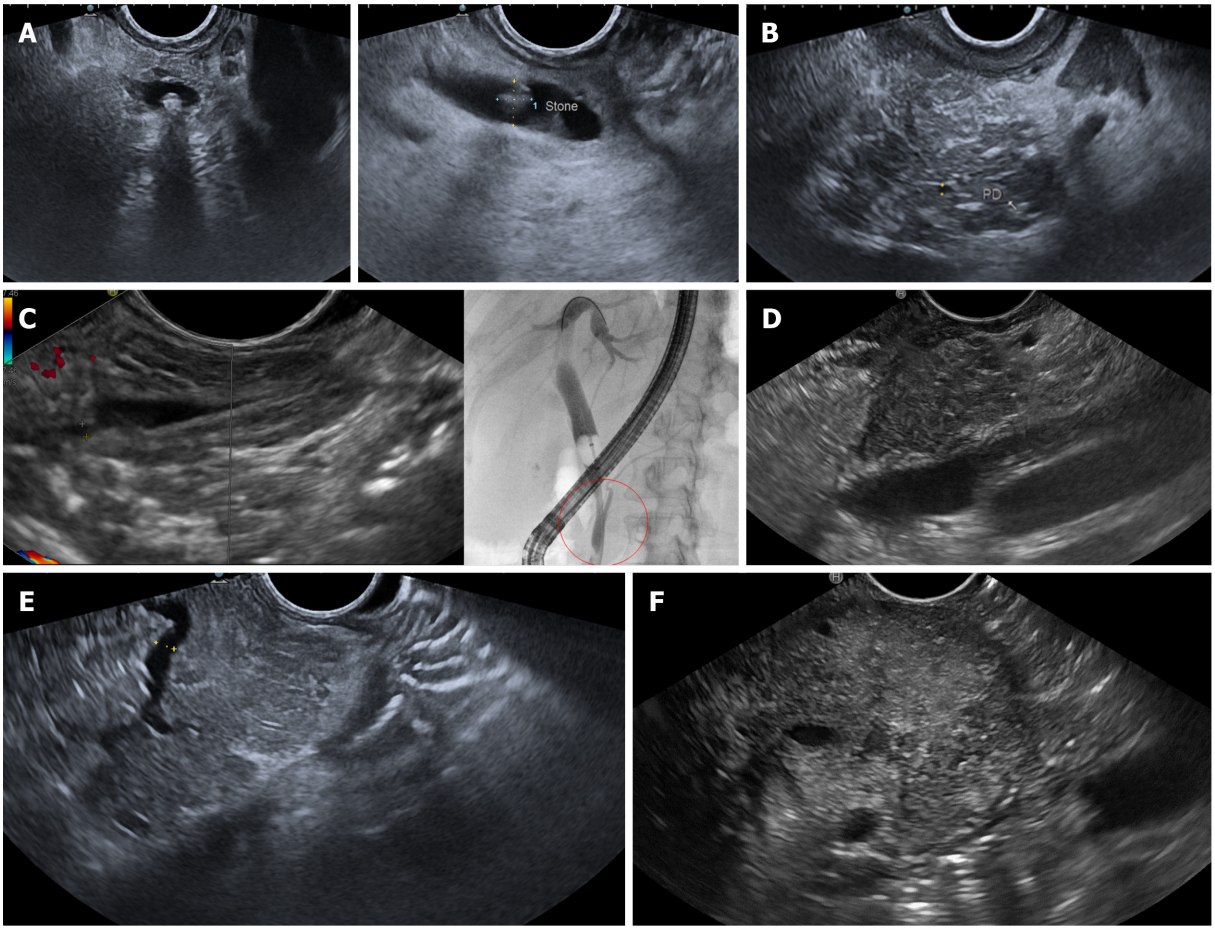

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Figure 1 Illustrative images of the main etiological diagnoses of acute pancreatitis obtained by endoscopic ultrasound. A: Choledocholithiasis: endoscopic ultrasound (EUS) images of a small (3-4 mm) shadowing stone located in the distal common bile duct, obtained from the bulb (on the left) and descending duodenum (on the right) stations; B: Early chronic pancreatitis: EUS image showed a lobular pancreatic parenchyma with hyperechoic strands and foci, with hyperechoic margins of the Wirsung's duct, all of which are minor criteria for chronic pancreatitis; C: Anomalous pancreaticobiliary junction: EUS image from the descending duodenum showed the confluence of Wirsung's duct and common bile duct into a long (15 mm) common channel (on the left). The anomaly was then confirmed by retrograde cholangiopancreatography (on the right), also showing lithiasis of the distal part of the common channel; D: Pancreatic lesion: EUS image of a small (15 mm) solid lesion located in the pancreatic head; the lesion appeared hypoechoic and with irregular / infiltrating margins and comes close to the portal venous confluence. Histology confirmed a pancreatic adenocarcinoma; E: Pancreas divisum: EUS image from the descending duodenum showed a dominant dorsal pancreatic duct (PD), draining in the minor papilla; F: Autoimmune pancreatitis: EUS image showed a diffuse hypoechoic pancreatic enlargement, with hypoechoic parenchymal margins, at the level of the body (clearly visible the splenic vessels on the left). After contrast enhancement, the pancreas showed homogeneous early hypervascularization. Histology obtained by fine-needle biopsy revealed inflammatory infiltrates, excluding cancer.

The percentage of types of EUS diagnosis after the different exam combinations are shown in Table 2.

Correlation between IAP diagnosis and clinical parameters

All patients without etiological diagnosis at EUS had no previous cholecystectomy compared to 28% with EUS diagnosis ($P = 0.028$). Patients with a final diagnosis of biliary pancreatitis had higher baseline median values of alanine aminotransferase (median value 154 *vs* 25, $P = 0.010$), aspartate aminotransferase (median value 95 *vs* 29, $P = 0.018$), direct bilirubin (median value 1.2 *vs* 0.6, $P = 0.015$), gamma-glutamyl transpeptidase (median value 180 *vs* 48, $P = 0.006$) and alkaline phosphatase (median value 150 *vs* 72, $P = 0.015$) compared to patients with non-biliary diagnosis. After differentiating between patients with or without previous cholecystectomy, these associations were maintained only for the non-cholecystectomy group. Noteworthy, when differentiating between first-episode and recurrent pancreatitis, chronic pancreatitis was the diagnosis at EUS in 21% and 82% of cases, respectively, a difference that was statistically significant ($P < 0.001$).

Etiology-based therapeutic intervention and follow-up data

During the follow-up, 12 out of the 16 patients diagnosed with biliary pancreatitis had evidence of choledocholithiasis; all of them underwent successful stone removal by endoscopic retrograde cholangiopancreatography (ERCP). Five out of the 25 patients with chronic pancreatitis underwent ERCP with pancreatic sphincterotomy (5/5) and pancreatic duct stenting (2/5) because of the evidence of

Table 2 Frequencies of acute pancreatitis etiologies at endoscopic ultrasound according to the type of previous negative exam/s

	Type of previous negative exam/s						
Type of AP etiology at EUS	US	CECT	MRCP	US + CECT	US + MRCP	CECT + MRCP	US + CECT + MRCP
Biliary; microlithiasis/biliary sludge	20%; 10%	16%; 5%	17%; 17%	19%; 7%	18%; 18%	14%; 14%	16%; 16%
Acute on chronic	37%	29%	38%	32%	39%	33%	37%
Solid or cystic lesions	15%	14%	17%	15%	18%	19%	21%
Pancreas divisum	3%	6%	4%	5%	4%	5%	5%
Anomalous pancreaticobiliary junction	6%	6%	4%	7%	4%	5%	5%
Autoimmune criteria	6%	3%	4%	5%	4%	5%	5%
Idiopathic	13%	26%	16%	17%	3%	9%	11%

AP: Acute pancreatitis; CECT: Contrast enhanced computed tomography; EUS: Endoscopic Ultrasound; MRCP: Magnetic resonance cholangiopancreatography; US: Ultrasound.

Wirsung's duct stenosis. Among the 11 patients with solid or cystic lesions as the cause of IAP, 4 were treated surgically, while the others were evaluated for a neoadjuvant or palliative approach. The 4 patients with features of autoimmune pancreatitis began steroid therapy with a good response.

During the follow-up time, a further episode of acute pancreatitis was observed in 3 patients (3.7%). Genetic tests for *CFTR*, *SPINK-1* and *PRSS1* mutations tested negative. All patients underwent EUS at recurrence. Two of these already had an EUS diagnosis of pancreas divisum and anomalous pancreatobiliary junction that were confirmed. The other had been initially diagnosed as idiopathic pancreatitis, which remained idiopathic even after the EUS examination performed after recurrence.

DISCUSSION

Our study investigated the role of EUS in the etiological diagnosis of IAP. Overall, the diagnostic yield of EUS for the identification of AP etiology was 80%, with 20% of patients with a final IAP diagnosis, which is in line with previous literature data[20,21]. This result is in keeping with two previous published meta-analyses reporting that EUS can detect a cause in most patients with IAP[8,22]. We found a high diagnostic gain of EUS after all combinations of previous negative cross-sectional techniques; interestingly, diagnostic gain remained remarkably high even after the combination of CECT and MRCP. This result supports EUS as the technique of choice after a negative CECT if the patient is suitable for endoscopic examination, while MRCP could be reserved for patients at elevated risk for invasive procedures.

The most common etiologies identified at EUS were lithiasis, acute on chronic pancreatitis and solid or cystic lesions. All the lithiasis identified at EUS after MRCP were microlithiasis/biliary sludge of gallbladder or common bile duct compared with about half after CECT; this finding confirms the superiority of EUS over MRCP in the identification of lithiasis of small size, as reported previously[9,21-24]. An increase in transaminases is known to have a high positive predictive value for gallstone pancreatitis[25]. Interestingly, in our study, patients with biliary pancreatitis showed higher levels of liver enzymes as compared to other types of diagnosis but only in the group without previous cholecystectomy, while patients with previous cholecystectomy showed similar median values of liver enzymes. This result seems to identify patients without prior cholecystectomy and with increased transaminases as those at greatest risk of biliary pancreatitis and suggests that these patients could benefit from EUS as the first diagnostic test, eventually followed by ERCP in the same session if the diagnosis is confirmed[26-28].

Chronic pancreatitis was the most frequent diagnosis overall, with similar frequencies after all combinations of previous cross-sectional imaging techniques. This data is in line with the current evidence that EUS has the highest diagnostic performance in the identification of chronic pancreatitis features[29,30]. This is especially true in the setting of early chronic pancreatitis where thanks to the high resolution, EUS may detect subtle parenchymal and ductal changes such as irregular ductal contour, side branch ectasia ≥1 mm and parenchymal lobularity, which are minor diagnostic criteria according to the Rosemont criteria[31-34]. When differentiating between single episode or recurrent pancreatitis at baseline, diagnosis of chronic pancreatitis was much more frequent in patients with recurrent forms; this result supports the use of EUS as the first diagnostic technique for the identification of AP etiology in this subgroup of patients.

Regarding solid lesions, all pancreatic carcinomas missed at CECT were 25 mm or less in size. This data agrees with previous evidence showing a superiority of EUS over CECT for the diagnosis of small pancreatic lesions[35-38]. Interestingly, the percentage of solid lesions identified at EUS was similar in groups with or without previous MRCP, suggesting that this technique does not improve the ability to diagnose small pancreatic lesions. The identification of solid pancreatic lesions, as well as cholelithiasis or choledocholithiasis, not seen at previous examinations is of paramount importance since it significantly changes the patient management and particularly the referral to surgery or ERCP. This is especially true for small pancreatic cancers, which may be suitable for curative treatment. Most cystic lesions were instead diagnosed after US and/or CECT failure. Indeed, as already demonstrated, MRCP and EUS have comparable diagnostic accuracy for the assessment of cystic lesions[39], although EUS can better identify some high-risk or worrisome features such as enhancing mural nodules or thickened or enhancing cyst walls[40].

Pancreatic duct anomalies, including pancreas divisum and anomalous pancreaticobiliary junction, were diagnosed at EUS in about 10% of cases. This percentage was the same even after the combination of CECT and MRCP, corroborating a high sensitivity of EUS in obtaining a detailed study of the distal portion of the pancreatic duct, as already reported in the literature[41,42]. In the meta-analysis by Wan *et al*[22], EUS and MRCP were equally effective in identifying pancreas divisum, while MRCP after secretin stimulation was superior to both techniques. However, due to increased costs and practical issues, secretin-enhanced MRCP has failed to gain widespread United States use across radiology practices[43] and is not routinely performed in our center.

Incidence of further AP episodes during the follow-up was low (3%) and related to non-modifiable causes (one idiopathic form and one pancreatic duct anomaly). The endoscopic treatment of all choledocholithiasis, followed by cholecystectomy when necessary, and of chronic pancreatitis when indicated may have contributed to reducing the risk of pancreatitis recurrence.

The strengths of the study were the homogeneity of the population, the availability of detailed clinical information and the availability of a long follow-up period after the treatment approach. The main limitations were the small sample size and the retrospective nature of the study, with the need of prospective, multicentric studies in order to delineate a diagnostic algorithm that optimizes the use of EUS in AP.

CONCLUSION

In conclusion, our study supports the role of EUS as the technique of choice in IAP after failure of one or more cross-sectional techniques including CECT and MRCP. We suggest the use of EUS as the first-level technique in patients presenting with increased liver enzymes and with no previous cholecystectomy and in the setting of recurrent pancreatitis. Given its high diagnostic yield, we also propose EUS as the first-line investigation in all suitable patients presenting with IAP. Finally, larger and prospective studies investigating not only the diagnostic but also the prognostic value of EUS in IAP are needed.

ARTICLE HIGHLIGHTS

Research background

Idiopathic acute pancreatitis (IAP) is a common condition and represents a diagnostic challenge because up to 20% of patients with IAP have recurrent episodes and may evolve to chronic pancreatitis. Endoscopic ultrasound (EUS) is highly effective in the etiological diagnosis of IAP, even after failure of a previous imaging technique. A significant proportion of AP remains idiopathic even after multiple imaging techniques, mainly including abdominal US, contrast-enhanced computed tomography (CECT) and magnetic resonance cholangiopancreatography (MRCP).

Research motivation

The role of EUS in IAP has been established by multiple studies, including meta-analyses. However, limited data are currently available about the diagnostic gain of EUS in cases of failure of multiple previous imaging techniques.

Research objectives

The primary aim of the study was to evaluate the diagnostic gain of EUS after failure of US, CECT and MRCP and particularly after different combination of these techniques. The secondary aims were to assess the overall EUS diagnostic yield in IAP, to associate the baseline clinical features with the specific IAP diagnosis and to analyze the frequency and types of AP recurrence during the follow-up.

Research methods

We performed a retrospective, single-center study. We enrolled all consecutive adult patients undergoing EUS for IAP over a 3-year period at the Ospedale Maggiore of Cremona. IAP was defined when a clear etiology could not be identified after a thorough medical history, complete blood tests and after performing at least one US, CECT or MRCP exam. The EUS diagnostic gain was calculated as the percentage of additional diagnoses obtained at EUS over the total number of patients undergoing US, CECT and/or MRCP.

Research results

Overall EUS diagnostic yield was 79%, with 21% of AP remaining idiopathic. This percentage is in line with the current literature. Gallstone disease and chronic pancreatitis were the most frequent diagnoses (20% and 31%, respectively). The EUS diagnostic gain over the associations of CECT + MRCP and US + CECT + MRCP was 63% and 68%, respectively. This is a relevant result that confirms the superiority of EUS in the etiological diagnosis of IAP, particularly in detecting microlithiasis and early signs of chronic pancreatitis. In patients without a previous cholecystectomy and with a final diagnosis of biliary pancreatitis, higher baseline median values of liver enzymes were found. Moreover, in patients with recurrent pancreatitis, chronic pancreatitis was the diagnosis in 82% of cases. These results suggest a high efficacy of EUS in the etiological diagnosis of IAP in patients without previous cholecystectomy and with recurrent pancreatitis. During a median follow-up of 31.5 mo, an additional episode of pancreatitis was observed in 3.7% of patients.

Research conclusions

EUS has a high diagnostic yield in IAP. About two-thirds of patients with IAP without etiological diagnosis with various combinations of US, CECT and MRCP received a diagnosis at EUS. This finding confirms the superiority of EUS over these techniques and proposes EUS as the investigation of first choice in all suitable patients. EUS shows the highest diagnostic gain in the setting of increased liver enzymes with no previous cholecystectomy and in the setting of recurrent pancreatitis.

Research perspectives

The role of EUS in the etiological diagnosis of IAP has been established by multiple studies including meta-analyses. Our study provided additional data supporting the high diagnostic gain of EUS in cases of failure of multiple previous imaging techniques. Future research should focus on the prognostic value of EUS in the setting of IAP, since patient management may change following the EUS diagnosis. Large multicentric and prospective studies addressing this issue are needed.

FOOTNOTES

Author contributions: All authors contributed to literature search and data collect; Mazza S, Elvo B and Grassia R wrote the paper; Mazza S and De Silvestri A performed the statistical analysis; Conti CB, Drago A, Verga MC, Soro S and Cereatti F critically revised the paper and contributed to the final version of the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Change point analysis validation of the learning curve in laparoscopic colorectal surgery: Experience from a non-structured training setting

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Abstract

BACKGROUND

The introduction of minimal invasive principles in colorectal surgery was a major breakthrough, resulting in multiple clinical benefits, at the cost, though, of a notably steep learning process. The development of structured nation-wide training programs led to the easier completion of the learning curve; however, these programs are not yet universally available, thus prohibiting the wider adoption of laparoscopic colorectal surgery.

AIM

To display our experience in the learning curve status of laparoscopic colorectal surgery under a non-structured training setting.

METHODS

We analyzed all laparoscopic colorectal procedures performed in the 2012-2019 period under a non-structured training setting. Cumulative sum analysis and change-point analysis (CPA) were introduced.

RESULTS

Overall, 214 patients were included. In terms of operative time, CPA identified the 110th case as the first turning point. A plateau was reached after the 145th case. Subgroup analysis estimated the 58th for colon and 52nd case for rectum operations as the respective turning points. A learning curve pattern was confirmed for pathology outcomes, but not in the conversion to open surgery and morbidity endpoints.

CONCLUSION

The learning curves in our setting validate the comparability of the results, despite the absence of National or Surgical Society driven training programs.

Key Words: Colorectal; Education; Gastrointestinal; Laparoscopy; Outcomes

Core Tip: In terms of operative time, the learning curve of a dedicated colorectal surgical team consists of three phases. Change point analysis identified the 110th case as the separation key-point of the first two phases. A plateau was reached after the 145th case. Although we were able to confirm the presence of a learning curve pattern in the histopathological endpoints, this was not the case for the open conversion and morbidity outcomes. Formal training program initiatives are necessary for the safe and efficient implementation of laparoscopic colorectal operations.

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INTRODUCTION

The introduction of minimal invasive principles in colorectal surgery, during the last two decades, was a major breakthrough[1]. Multiple studies confirmed the advantages of a minimal invasive approach, including reduced analgesic requirements, fewer complications, and a shorter recovery period[2].

Nonetheless, the accrual of these benefits depends on the completion of an elongated learning process [3-5]. Due to the complexity of laparoscopic colorectal operations (LCRO) and the innate dexterity requirements, the accumulation of the respective surgical skills is quite demanding[6-9]. Thus, like other multi-leveled procedures, learning curves were universally adopted for the assessment of surgical competency[10-13].

Although there is a remarkable heterogeneity in the turning points of learning curves for LCRO, current evidence suggests that at least 100 consecutive operations are needed to obtain proficiency[14-17]. During the initial phase, an analogous variation in endpoints, such as morbidity and open conversion rates, is expected[3,18-24].

The determination of the individual elements that contribute to the elongation of the learning curve was a major step towards the establishment of a safety and training culture in laparoscopic colorectal surgery[14,23,25]. Subsequently, the development of structured nation-wide training programs expedited the completion of the respective learning curves[26-28]. Among the various components of these programs are the formation of specialized colorectal surgical groups, the conduction of hands-on courses, and the introduction of mentor guidance during the first cases[26-29]. Unfortunately, these initiatives are not yet implemented in all health systems, thus restraining the efficient dissemination of the minimal invasive principles in colorectal surgery[9,24,30].

Therefore, we designed this study to analyze the laparoscopic colorectal surgery learning curves, outside a formal national or surgical society driven training program.

MATERIALS AND METHODS

This study is a retrospective analysis of a prospectively collected database. Between January 2012 and December 2019, data from all laparoscopic colorectal resections performed by a specialized colorectal surgical team, were recorded in an institutional database. All patients, prior to their inclusion, provided informed consent for data recording, analyses, and future publication. This study report follows the STROBE guidelines[31].

The surgical team consisted of two consultant surgeons with previous experience in laparoscopic general surgery (G.T. and I.B.). Six months prior to the onset of the study, the surgeons attended both national and international specialized formal courses and performed their initial operations under proctoring. However, this learning process was not based on any national or scientific society training program, due to the absence of such initiatives in Greece. The surgical team was also supported by a dedicated pathology team responsible for the evaluation of the resected specimens.

All operations were performed with four or five trocars. Dissection was completed using an energy source. A medial to lateral approach was implemented in all patients. In case of malignancy, the appropriate oncological principles (Complete mesocolic excision/ Total mesorectal excision CME/TME and Central vascular ligation CVL) were followed. Splenic flexure mobilization was always performed in left sided tumors. A structured pathology report was also provided.

All adult patients (age > 18 years) submitted to elective or semi-elective laparoscopic colorectal surgery for benign or malignant disease were deemed as eligible. The following exclusion criteria were considered: (1) Age < 18 years; (2) American Society of Anesthesiologists (ASA) score > III; (3) Emergency surgery, *e.g.*, for peritonitis and perforation; and (4) Cases not performed by the above-mentioned surgical team.

The primary endpoint of our study was to identify the learning curve status of the operation duration in patients submitted to LCRO. Subgroup analysis for colon (LCO) and rectal operations (LRO) was also performed. Secondary endpoints included operative characteristics (complication and open conversion rates) and specimen pathology quality outcomes. Postoperative complications were any Clavien Dindo ≥ 2 adverse events. The complexity of each operation was graded on the basis of the Miskovic *et al*[23] classification system. Data extraction was completed by a group of senior researchers (I.M., G.V., and A.V.).

Statistical analysis

Prior to any statistical analysis, a Shapiro-Wilk normality test was applied to all continuous variables. Since normality was not proven, a non-parametric approach was implemented. Mann-Whitney *U* test was used for the comparison of continuous variables. Kruskal Wallis *H* test was applied in multiple comparisons of continuous data. Categorical variables were analyzed by Pearson chi square test, while proportions were evaluated by the *Z* test. Correlation was assessed through a Spearman's rank-order correlation test.

To identify variations in the changing rate of the studied variables and plot the respective learning curve (LC), cumulative sum (CUSUM) analysis was performed. CUSUM analysis was applied to all above-mentioned endpoints.

The CUSUM analysis plots that confirmed a significant LC pattern, were further evaluated by change-point analysis (CPA). CPA allows the identification of even small trend shifts and provides the respective statistical significance of each change. The CPA analysis incorporated the application of 1000 bootstraps, and a 50% confidence level (CL) for candidate changes.

The acceptable rate of missing values was < 10%. Missing data were handled using the multiple imputation technique. Continuous data are reported in the form of median (interquartile range), whereas categorical variables are provided as number (percentage). Significance was considered at the level of $P < 0.05$. Statistical analyses were completed with STATA v.13 and SPSS v.23 software.

RESULTS

Patient characteristics are summarized in Table 1. Overall, 214 LCRO were included in the study. More specifically, 76 (35.5%) right colectomies, 31 (14.5%) left colectomies, 26 (12.2%) sigmoidectomies, 72 (33.6%) low anterior resections (LAR), 7 (3.3%) ultra-LAR, and 2 (2.4%) abdominoperineal resections (APR) were performed. Most of the cases displayed a level 1 (54.2%) or 2 (38.2%) complexity. Mean operation duration was 180 and 200 min for LCO and LRO, respectively. The results of the correlation analyses are reported in Supplementary Tables. The overall complication rate was 22.9%. Negative resection margins were confirmed in 95.3% of the patients. A mesocolic and mesorectal resection plane was achieved in 86.4% and 88.8% of cases, respectively.

Figure 1 illustrates the LCRO learning curve, in terms of operation duration. A declining trend of the CUSUM plot, until the 109th case was noted, followed by an upwards shift and a maximum value at the 176th case. CPA confirmed the 110th (CL: 100%) and 145th (CL: 99%) case turning points. On the basis of these findings (Table 2), the LCRO LC was subdivided in three distinct phases (phase I: 1 to 109 operations; phase II: 110 to 144 operations; and phase III: 145 to 214 operations).

Figures 2 and 3 display the learning curve plots of LCO and LRO, correspondingly. Both LC patterns were comparable. First successive cases resulted in a gradual decrease and the reach of a minimum, followed by a consequent increment of the LC line. We confirmed that the 58th (CL: 99%) and 52nd (CL: 100%) cases were the corresponding turning points of colon and rectal resections. Hence, we identified two phases of the LCO and LRO learning curve (LCO phase I: 1 to 57 operations; LCO phase II: 58 to 133 operations; LRO phase I: 1 to 51 operations; LRO phase II: 52 to 81 operations).

Table 2 summarizes the eligible patient data and the study outcomes between the various LC phases. LCRO phase III displayed a significant improvement in the specimen length ($P < 0.001$), the resection distal margin ($P < 0.001$), and the lymph node yield ($P = 0.016$).

Subgroup analyses of the LC phases showed that surgical experience was correlated with the specimen length in both LCO and LRO ($P = 0.001$ and $P < 0.001$, respectively). However, dexterity in laparoscopic surgery increased the distal resection margin ($P < 0.001$) and number of excised lymph

Table 1 Patient characteristics

		Total	Colon operations	Rectal operations	*P* value
n		214	133	81	
Sex	Male	128 (59.8%)	78 (58.6%)	50 (61.7%)	NS
	Female	86 (40.2%)	55 (41.4%)	31 (38.3%)	
Age (yr)		70 (13)	71 (14)	68 (13)	NS
BMI (kg/m^2)		27 (5)	28 (5)	26.5 (4)	NS
ASA score	I	71 (33.2%)	35 (26.3%)	36 (44.4%)	0.021
	II	117 (54.7%)	79 (59.4%)	38 (46.9%)	
	III	26 (12.1%)	19 (14.3%)	7 (8.6%)	
Diagnosis	Malignancy	206 (96.3%)	125 (94%)	81 (100%)	NS
	Diverticulitis	6 (2.8%)	6 (4.5%)	0 (0%)	
	Volvulus	1 (0.5%)	1 (0.8%)	0 (0%)	
	Crohn's disease	1 (0.5%)	1 (0.8%)	0 (0%)	
Previous operation		17 (7.9%)	13 (9.8%)	4 (4.9%)	NS
T	1	51 (24.8%)	33 (26.4%)	18 (22.2%)	NS
	2	63 (30.6%)	39 (31.2%)	24 (29.6%)	
	3	85 (41.3%)	47 (37.6%)	38 (46.9%)	
	4	7 (3.4%)	6 (4.8%)	1 (1.2%)	
N	0	153 (74.3%)	89 (71.2%)	64 (79%)	NS
	1	42 (20.4%)	30 (24%)	12 (14.8%)	
	2	11 (5.3%)	6 (4.8%)	5 (6.2%)	
M	0	205 (99.5%)	125 (100%)	80 (98.8%)	NS
	1	1 (0.5%)	0 (0%)	1 (1.2%)	
Neoadjuvant modality		19 (9.2%)	2 (1.6%)	17 (20%)	< 0.001
Complexity level	1	116 (54.2%)	74 (55.6%)	42 (51.9%)	0.022
	2	82 (38.2%)	44 (33.1%)	38 (46.9%)	
	3	6 (2.8%)	6 (4.5%)	0 (0%)	
	4	10 (4.7%)	9 (6.8%)	1 (1.2%)	
Operation	Right colectomy	76 (35.5%)	76 (57.1%)	-	< 0.001
	Left colectomy	31 (14.5%)	31 (23.3%)	-	
	Sigmoidectomy	26 (12.1%)	26 (19.5%)	-	
	Low anterior resection	72 (33.6%)	-	72 (88.9%)	
	Ultra-low anterior resection	7 (3.3%)	-	7 (8.6%)	
	Abdominoperineal resection	2 (1%)	-	2 (2.4%)	
Emergency status	Elective	212 (99.1%)	131 (98.5%)	81 (100%)	NS
	Semi-elective	2 (0.9%)	2 (1.5%)	0 (0%)	
Laparoscopic approach	Totally laparoscopic	182 (85%)	127 (95.5%)	55 (67.9%)	< 0.001
	Laparoscopy assisted	32 (15%)	6 (4.5%)	26 (32.1%)	
Preoperative optimization	Bowel preparation	191 (89.3%)	112 (84.2%)	79 (97.5%)	0.002
	Antibiotic preparation	206 (96.3%)	127 (95.5%)	79 (97.5%)	NS
	Tattoo	51 (23.8%)	28 (21.1%)	23 (28.4%)	NS
Extraction site	Pfannenstiel	95 (44.4%)	40 (30.1%)	55 (67.9%)	< 0.001

	Subumbilical	19 (8.9%)	4 (3%)	15 (18.5%)	
	Transumbilical	100 (46.7%)	89 (66.9%)	11 (13.6%)	
Anastomosis	Stapled	159 (75%)	80 (60.2%)	79 (100%)	< 0.001
	Handsewn	53 (25%)	53 (39.8%)	0 (0%)	
	Intracorporeal	112 (52.8%)	50 (37.6%)	62 (78.4%)	< 0.001
	Extracorporeal	100 (47.1%)	83 (62.4%)	17 (21.5%)	
	Protective stoma	66 (30.8%)	9 (6.8%)	57 (70.4%)	< 0.001
Operation duration (min)		180 (51)	180 (50)	200 (60)	< 0.001
Open conversion		20 (9.3%)	6 (4.5%)	14 (17.3%)	0.002
Transfusion		8 (3.7%)	4 (3%)	4 (4.9%)	NS
Tumor diameter (cm)		3 (2.2)	3 (2)	3.75 (2.5)	NS
Specimen length (cm)		20 (9)	21 (7)	15 (7)	< 0.001
Distal margin (cm)		5 (4.35)	5.25 (3.5)	4.5 (4.25)	0.01
Lymph nodes		17 (12)	19 (13)	15 (11)	0.004
Lymph node ratio		0 (2.3)	0 (4)	0 (0)	NS
Histological grade	1	40 (19.4%)	20 (16%)	20 (24.7%)	NS
	2	135 (65.5%)	89 (71.2%)	46 (56.8%)	
	3	31 (15%)	16 (12.8%)	15 (18.5%)	
R status	0	204 (95.3%)	124 (99.2%)	80 (98.8%)	NS
	1	2 (0.9%)	1 (0.8%)	1 (1.2%)	
Resection plane	Mesocolic/mesorectal	183 (88.8%)	108 (86.4%)	75 (88.8%)	NS
	Intramesocolic/intramesorectal	19 (9.2%)	14 (11.2%)	5 (6.2%)	
	Muscularis propria	4 (1.9%)	3 (2.4%)	1 (1.2%)	
Extramural vascular invasion		54 (26.2%)	33 (26.4%)	21 (25.9%)	NS
Perineural invasion		21 (10.2%)	13 (10.4%)	8 (9.9%)	NS
Mucous	Focal	29 (14.1%)	20 (16%)	9 (11.1%)	NS
	Diffuse	20 (9.7%)	15 (12%)	5 (6.2%)	
Complications	Total	49 (22.9%)	33 (24.8%)	16 (19.8%)	NS
	Wound infection	9 (4.2%)	5 (3.8%)	4 (4.9%)	NS
	Wound dehiscence	2 (0.9%)	2 (1.5%)	0 (0%)	
	Leak	14 (6.5%)	10 (7.5%)	4 (4.9%)	
	Postoperative ileus	11 (5.1%)	8 (6%)	3 (3.7%)	
	Urinary tract infection	2 (0.9%)	0 (0%)	2 (2.5%)	
	Urinary retention	2 (0.9%)	1 (0.8%)	1 (1.2%)	
	Bleeding	3 (1.4%)	1 (0.8%)	2 (2.5%)	
	Pulmonary embolism	2 (0.9%)	2 (1.5%)	0 (0%)	
	ARDS	1 (0.5%)	0 (0%)	1 (1.2%)	
	Other	4 (1.9%)	4 (3%)	0 (0%)	
Relaparotomy		11 (5.1%)	8 (6%)	3 (3.7%)	NS
ICU		8 (3.7%)	5 (3.8%)	3 (3.7%)	NS
Mortality		5 (2.3%)	4 (3%)	1 (1.2%)	NS
Length of hospital stay (d)		6 (2)	6 (2)	6 (2)	NS
Follow-up (mo)		2 (3.75)	2 (5.8)	2 (2.5)	NS

NS: Non-significant; BMI: Body mass index; ASA: American Society of Anesthesiologists; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit.

nodes (P = 0.002) only in LCO.

Postoperative complication analysis (Supplementary Figures) in LCRO (P = 0.48), LCO (P = 0.419), and LRO (P = 0.521) did not identify an LC pattern. Similarly, open conversion was not associated with a learning curve pattern in any of the study subgroups (P = 0.3, P = 0.8, and P = 0.19, correspondingly).

Finally, the diagrams of the pathology endpoints are provided in Supplementary Figures. The 64th case (CL: 100%) was estimated as the turning point of the specimen length in colon resections. A plateau was reached after the 99th case (CL: 94%). The respective turning point of the LRO was the 47th case. There were no significant CPA turning points in the resected lymph node yield.

DISCUSSION

LC is defined as the schematic depiction of the fluctuation of an efficiency outcome, plotted over a successive number of repetitions[27,29]. Among the various statistical methodologies that have been employed for the LC evaluation are the group splitting, moving average, and CUSUM analysis[3,17,32,33]. Following an introductory learning phase, the trainee is gradually performing operations of higher complexity and difficulty[34,35]. Finally, once the iteration of the process does not affect the measured variable, mastery is achieved[16,17,32]. As a result, estimation of the LC turning points is of paramount importance in trend analysis[26].

The inherent divergence of the learning efficiency, alongside the discrepancy in the estimated LC endpoints, resulted in a significant heterogeneity in the published LC outcomes[4,36]. To be more specific, recent studies in laparoscopic colorectal surgery suggested that LC turning points fluctuate between 10[32] and 200 cases[37].

Operation duration has been frequently introduced as the LCRO LC estimated variable[27,29,32]. Nonetheless, surgical expertise assessment, based solely upon operation duration, may result in biased conclusions[27,29]. This is due to the fact that the overlapping surgical skills and the efficient collaboration between the assisting theater personnel can also impact the duration of a procedure[27,38,39]. Initial studies suggested that 23 operations may suffice for the standardization of operative time[9,24]; however, this was not validated in subsequent trials, where a 96-case margin was reported[23]. Our results estimated the first LC cut-off point at the 110th case, which is in parallel with the previous evidence.

Interestingly, we identified lower LC turning points during the individual assessment of both colon and rectal operations (LCO: 58 cases; LRO: 52 cases). This discrepancy may be the result of the combination of the two study subgroups. In particular, the estimated LC of a specific operation subtype is usually shorter, since it incorporates fewer surgical steps. Despite the fact that previous surgical competence, in either LCO or LRO, may accelerate the transposition of skills to the other, completion of LCRO LC prerequisites the attainment of mastery in both operations. Therefore, LCRO LC is equal to the summation of the two subgroup CUSUM plots.

The narrow working space, the lack of three-dimensional vision, and the fixed port positions further enhance the LCRO surgical complexity and the risk of critical intraoperative events[29]. Consequently, the learning curve status mat have a direct impact on perioperative morbidity[7,17,22,23]. Previous reports estimated that a plateau in LCRO complication rate is achieved after 140 to 200 operations[23,37]. However, we were not able to validate a LC pattern in perioperative morbidity. Similarly, MacKenzie *et al*[4] suggested the absence of fluctuation in the perioperative complications rate during the LC period. Nonetheless, these results may be due to an inadequate sample size, since larger cohorts confirmed the presence of an LC pattern in perioperative morbidity[7,17,22,23,37].

Open conversion is considered in the case of a critical event that is not amendable by the ongoing approach[17,19,32]. Typical examples include an intraoperative complication or the compromise of the oncological principles[15,19,24,25]. Although not widely accepted, conversion turning point is estimated at 61 successive operations[18,26,40]. A structured training program, though, may further reduce the above-mentioned LC margin[18,26,40]. Even though our results were in accordance with previously published reports[23], we did not confirm the presence of an LC trend in the open conversion rate.

Specimen-related endpoints are of paramount importance when evaluating the oncological efficacy of an operation[6,14,36]; lymph node yield is the most prominent among them[6,14,36]. However, this can be misleading since lymph node harvest can be affected by anthropometric and disease-related characteristics[41]. Despite these, we confirmed the presence of a significant LC trend in the number of the resected lymph nodes. Additionally, CPA validated the increase of the specimen length after the 64th LCO and 47th LRO case, respectively. We did not introduce positive resection margin and non-CME/TME dissection plane as an LC outcome, due to the scarcity of these events. Moreover, in case of CME/ TME violation, an open conversion was performed to secure adherence to oncological principles.

Table 2 Patient characteristics in different phases of the learning curve

		Overall				Colon			Rectal		
		Phase I (1-109)	Phase II (110-144)	Phase III (145-214)	*P* value	Phase I (1-57)	Phase II (58-133)	*P* value	Phase I (1-51)	Phase II (52-81)	*P* value
N		109	35	70		57	76		51	30	
Sex	Male	68 (62.4%)	24 (68.6%)	36 (51.4%)	NS	37 (64.9%)	41 (53.9%)	NS	30 (58.8%)	20 (66.7%)	NS
	Female	41 (37.6%)	11 (31.4%)	34 (48.6%)		20 (35.1%)	35 (46.1%)		21 (41.2%)	10 (33.3%)	
Age (yr)		71.5 (12)	70 (13)	69.5 (14)	NS	72 (14)	71 (13)	NS	69.5 (12)	67 (16)	NS
BMI (kg/m^2)		27 (5)	28 (4)	27 (5)	NS	28 (6)	28 (5)	NS	26 (3)	27.5 (6)	NS
ASA score	I	36 (33%)	13 (37.1%)	22 (31.4%)	NS	14 (24.6%)	21 (27.6%)	NS	21 (41.2%)	15 (50%)	NS
	II	62 (56.9%)	16 (45.7%)	39 (55.7%)		35 (61.4%)	44 (57.9%)		27 (52.9%)	11 (36.7%)	
	III	11 (10.1%)	6 (17.1%)	9 (12.9%)		8 (14%)	11 (14.5%)		3 (5.9%)	4 (13.3%)	
Diagnosis	Malignancy	106 (97.2%)	34 (97.1%)	66 (94.3%)	NS	54 (94.7%)	71 (93.4%)	NS	51 (100%)	30 (100%)	-
	Diverticulitis	2 (1.8%)	1 (2.9%)	3 (4.3%)		2 (3.5%)	4 (5.3%)		-	-	
	Volvulus	1 (0.9%)	0 (0%)	0 (0%)		1 (1.8%)	0 (0%)		-	-	
	Crohn's disease	0 (0%)	0 (0%)	1 (1.4%)		0 (0%)	1 (1.3%)		-	-	
Previous operation		13 (11.9%)	2 (5.7%)	2 (2.9%)	NS	9 (15.8%)	4 (5.3%)	0.04	4 (7.8%)	0 (0%)	NS
T	1	24 (22.6%)	6 (17.6%)	21 (31.8%)	NS	12 (22.6%)	21 (29.2%)	NS	12 (23.5%)	6 (20%)	NS
	2	34 (32.1%)	7 ((20.6%)	22 (33.3%)		16 (30.2%)	23 (31.9%)		18 (35.3%)	6 (20%)	
	3	43 (40.6%)	20 (58.8%)	22 (33.3%)		21 (39.6%)	26 (36.1%)		20 (39.2%)	18 (60%)	
	4	5 (4.7%)	1 (2.9%)	1 (1.5%)		4 (7.5%)	2 (2.8%)		1 (2%)	0 (0%)	
N	0	77 (74.5%)	25 (73.5%)	49 (74.2%)	NS	36 (67.9%)	53 (73.6%)	NS	41 (80.4%)	23 (76.7%)	NS
	1	23 (21.7%)	6 (17.6%)	13 (19.7%)		16 (30.2%)	14 (19.4%)		6 (13.7%)	5 (16.7%)	
	2	4 (3.8%)	3 (8.8%)	4 (6.1%)		1 (1.9%)	5 (6.9%)		3 (5.9%)	2 (6.7%)	
M	0	106 (100%)	34 (100%)	65 (98.5%)	NS	53 (100%)	72 (100%)	-	51 (100%)	29 (96.7%)	NS
	1	0 (0%)	0 (0%)	1 (1.5%)		-	-		0 (0%)	1 (3.3%)	
Neoadjuvant modality		6 (5.5%)	5 (14.3%)	8 (11.4%)	NS	0 (0%)	2 (2.6%)	NS	6 (11.8%)	11 (36.7%)	0.008
Complexity level	1	50 (54.1%)	13 (37.1%)	44 (62.9%)	NS	29 (50.9%)	45 (59.2%)	NS	30 (58.8%)	12 (40%)	NS
	2	42 (38.5%)	20 (57.1%)	20 (28.6%)		21 (36.8%)	23 (30.3%)		20 (39.2%)	18 (60%)	

	3	2 (1.8%)	1 (2.9%)	3 (4.3%)		2 (3.5%)	4 (5.3%)		0 (0%)	0 (0%)	
	4	6 (5.5%)	1 (2.9%)	3 (4.3%)		5 (8.8%)	4 (5.3%)		1 (2%)	0 (0%)	
Operation	Right colectomy	34 (31.2%)	13 (37.1%)	29 (41.4%)	NS	34 (59.6%)	42 (55.3%)	NS	-	-	NS
	Left colectomy	10 (9.2%)	6 (17.1%)	15 (21.4%)		10 (17.5%)	21 (27.6%)		-	-	
	Sigmoidectomy	13 (11.9%)	2 (5.7%)	11 (15.7%)		13 (22.8%)	13 (17.1%)		-	-	
	Low anterior resection	46 (42.2%)	13 (37.1%)	13 (18.6%)		-	-		45 (88.2%)	27 (90%)	
	Ultra-low anterior resection	4 (3.7%)	1 (2.9%)	2 (2.9%)		-	-		4 (7.8%)	3 (10%)	
	Abdominoperineal resection	2 (1.8%)	0 (0%)	0 (0%)		-	-		2 (4%)	0 (0%)	
Emergency status	Elective	109 (100%)	35 (100%)	68 (97.1%)	NS	57 (100%)	74 (97.4%)	NS	51 (100%)	30 (100%)	-
	Semi-elective	0 (0%)	0 (0%)	2 (2.9%)		0 (0%)	2 (2.6%)		-	-	
Laparoscopic approach	Totally laparoscopic	98 (89.9%)	24 (68.6%)	60 (85.7%)	0.009	56 (98.2%)	71 (93.4%)	NS	41 (80.4%)	14 (46.7%)	0.002
	Laparoscopy assisted	11 (10.1%)	11 (31.4%)	10 (14.3%)		1 (1.8%)	5 (6.6%)		10 (19.6%)	16 (53.3%)	
Preoperative optimization	Bowel preparation	107 (98.2%)	30 (85.7%)	54 (77.1%)	< 0.001	56 (98.2%)	56 (73.7%)	< 0.001	50 (98%)	29 (96.7%)	NS
	Antibiotic preparation	105 (96.3%)	33 (94.3%)	68 (97.1%)	NS	54 (94.7%)	73 (96.1%)	NS	50 (98%)	29 (96.7%)	NS
	Tattoo	36 (33%)	2 (5.7%)	13 (18.6%)	0.002	17 (29.8%)	11 (14.5%)	0.032	19 (37.3%)	4 (13.3%)	0.021
Extraction site	Pfannenstiel	52 (47.7%)	15 (42.9%)	28 (40%)	NS	15 (26.3%)	25 (32.9%)	NS	37 (72.5)	18 (60%)	NS
	Subumbilical	12 (11%)	4 (11.4%)	3 (4.3%)		2 (3.5%)	2 (2.6%)		9 (17.6%)	6 (20%)	
	Transumbilical	45 (41.3%)	16 (45.7%)	39 (55.7%)		40 (70.2%)	49 (64.5%)		5 (9.8%)	6 (20%)	
Anastomosis	Stapled	85 (78.7%)	24 (70.6%)	50 (71.4%)	NS	34 (59.6%)	46 (60.5%)	NS	50 (100%)	29 (100%)	NS
	Handsewn	23 (21.3%)	10 (29.4%)	20 (28.6%)		23 (40.4%)	30 (39.5%)		0 (0%)	0 (0%)	
	Intracorporeal	57 (52.8%)	16 (47.1%)	39 (55.7%)	NS	18 (31.6%)	32 (42.1%)	NS	38 (76%)	24 (82.8%)	NS
	Extracorporeal	51 (47.2%)	18 (52.9%)	31 (44.3%)		39 (68.4%)	44 (57.9%)		12 (24%)	5 (17.2%)	
	Protective stoma	38 (34.9%)	11 (31.4%)	17 (24.3%)	NS	3 (5.3%)	6 (7.9%)	NS	34 (66.7%)	23 (76.7%)	NS
Operation duration (min)		180 (50)	220 (60)	180 (40)	< 0.001	160 (48)	180 (40)	0.003	200 (50)	220 (63)	0.003
Open conversion		13 (11.9%)	2 (5.7%)	5 (7.1%)	NS	4 (7%)	2 (2.6%)	NS	8 (15.7%)	6 (20%)	NS
Transfusion		5 (4.6%)	0 (0%)	3 (4.3%)	NS	3 (5.3%)	1 (1.3%)	NS	1 (2%)	3 (10%)	NS
Tumor diameter (cm)		3 (2.1)	4 (2.4)	3 (2)	NS	3 (1.5)	3.5 (2)	NS	4 (2.4)	3 (3)	NS
Specimen length (cm)		16.25 (7.25)	22.5 (6.5)	24 (8)	< 0.001	20.5 (8)	23 (8.75)	0.001	14.25 (3.75)	21 (6)	< 0.001

Distal margin (cm)		4 (3.5)	7 (2)	7 (5)	< 0.001	4 (2.5)	7 (3.5)	< 0.001	4 (4.25)	5 (4.5)	NS
Lymph nodes		15 (10)	20 (19)	21 (12)	0.016	15 (10)	22 (13)	0.002	15 (10)	12.5 (15)	NS
Lymph node ratio		0 (0)	0 (0.8)	0 (8)	NS	0 (4.5)	0 (3.8)	NS	0 (0)	0 (13.5)	NS
Histological grade	1	26 (24.5%)	1 (2.9%)	13 (19.7%)	0.013	10 (18.9%)	10 (13.9%)	0.009	16 (31.4%)	4 (13.3%)	NS
	2	60 (56.6%)	27 (79.5%)	48 (72.7%)		31 (58.5%)	58 (80.6%)		27 (52.9%)	19 (63.3%)	
	3	20 (18.9%)	6 (17.6%)	5 (7.6%)		12 (22.6%)	4 (5.6%)		8 (15.7%)_	7 (23.3%)	
R status	0	105 (99.1%)	33 (97.1%)	66 (100%)	NS	53 (98.1%)	71 (100%)	NS	51 (100%)	29 (96.7%)	NS
	1	1 (0.9%)	1 (2.9%)	0 (0%)		1 (1.9%)	0 (0%)		0 (0%)	1 (3.3%)	
Resection plane	Mesocoli/mesorectal	91 (85.8%)	31 (91.2%)	61 (92.4%)	NS	43 (79.6%)	65 (91.5%)	NS	47 (92.2%)	28 (93.3%)	NS
	Intramesocolic/intramesorectal	12 (11.3%)	3 (8.8%)	4 (6.1%)		9 (16.7%)	5 (7%)		3 (5.9%)	2 (6.7%)	
	Muscularis propria	3 (2.8%)	0 (0%)	1 (1.5%)		2 (3.7%)	1 (1.4%)		1 (2%)	0 (0%)	
Extramural vascular invasion		30 (28.3%)	7 (20.6%)	17 (25.8%)	NS	13 (24.5%)	20 (27.8%)	NS	16 (31.4%)	5 (16.7%)	NS
Perineural invasion		13 (12.3%)	4 (11.8%)	4 (6.1%)	NS	7 (13.2%)	6 (8.3%)	NS	6 (11.8%)	2 (6.7%)	NS
Mucous	Focal	11 (10.4%)	12 (35.3%)	6 (9.1%)	0.006	6 (11.3%)	14 (19.4%)	NS	4 (7.8%)	5 (16.7%)	NS
	Diffuse	9 (8.5%)	3 (8.8%)	8 (12.1%)		7 (13.2%)	8 (11.1%)		2 (3.9%)	3 (10%)	
Complications	Total	28 (25.7%)	9 (25.7%)	12 (17.1%)	NS	15 (26.3%)	18 (23.7%)	NS	12 (23.5%)	4 (13.3%)	NS
	Wound infection	5 (4.6%)	2 (5.7%)	2 (2.9%)	NS	1 (1.8%)	4 (5.3%)	NS	4 (7.8%)	0 (0%)	NS
	Wound dehiscence	1 (0.9%)	1 (2.9%)	0 (0%)		1 (1.8%)	1 (1.3%)		0 (0%)	0 (0%)	
	Leak	8 (7.3%)	4 (11.4%)	2 (2.9%)		5 (8.8%)	5 (6.6%)		2 (3.9%)	2 (6.7%)	
	Postoperative ileus	7 (6.4%)	1 (2.9%)	3 (4.3%)		4 (7%)	4 (5.3%)		3 (5.9%)	0 (0%)	
	Urinary tract infection	2 (1.8%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)		2 (3.9%)	0 (0%)	
	Urinary retention	1 (0.9%)	0 (0%)	1 (1.4%)		0 (0%)	1 (1.3%)		1 (2%)	0 (0%)	
	Bleeding	1 (0.9%)	0 (0%)	2 (2.9%)		0 (0%)	1 (1.3%)		1 (2%)	1 (3.3%)	
	Pulmonary embolism	1 (0.9%)	1 (2.9%)	0 (0%)		1 (1.8%)	1 (1.3%)		0 (0%)	0 (0%)	
	ARDS	0 (0%)	0 (0%)	1 (1.4%)		0 (0%)	0 (0%)		0 (0%)	1 (3.3%)	
	Other	3 (2.8%)	0 (0%)	1 (1.4%)		3 (5.3%)	1 (1.3%)		0 (0%)	0 (0%)	
Relaparotomy		5 (4.6%)	3 (8.6%)	3 (4.3%)	NS	2 (3.5%)	6 (7.9%)	NS	2 (3.9%)	1 (3.3%)	NS
ICU		6 (5.5%)	1 (2.9%)	1 (1.4%)	NS	4 (7%)	1 (1.3%)	NS	2 (3.9%)	1 (3.3%)	NS

Mortality	4 (3.7%)	1 (2.9%)	0 (0%)	NS	3 (5.3%)	1 (1.3%)	NS	1 (2%)	0 (0%)	NS
Length of hospital stay (d)	6 (2)	6 (3)	6 (2)	NS	6 (2)	6 (2)	NS	6 (2)	5 (1)	NS
Follow-up (mo)	2 (3.25)	0.65 (0)	6 (5)	NS	2 (3.3)	6.8 (4.4)	NS	2 (3)	0.27 (0)	0.032

BMI: Body mass index; ASA: American Society of Anesthesiologists; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit.

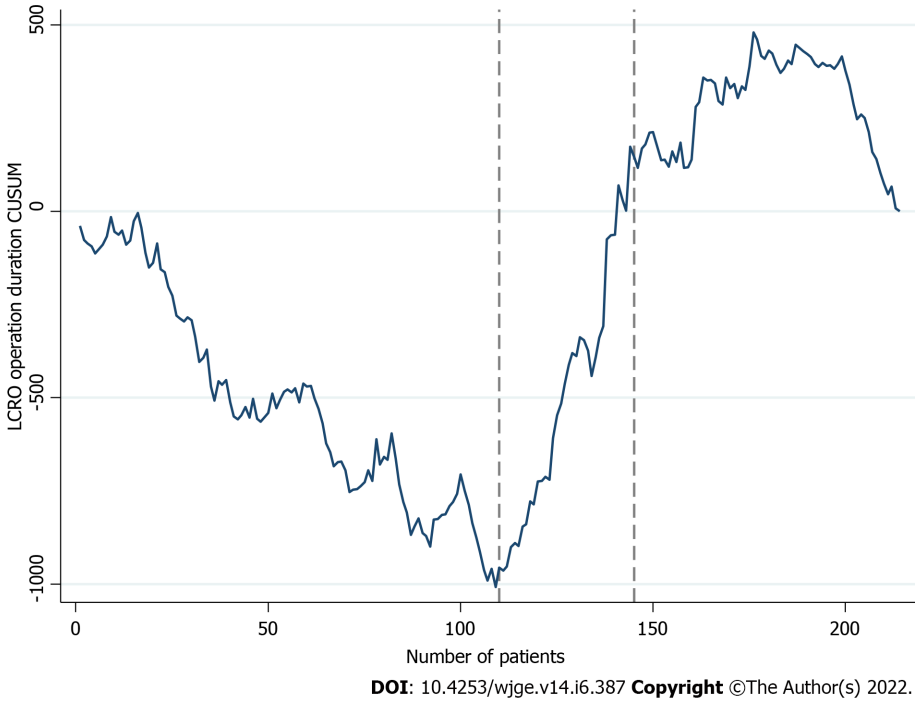
A swift completion of the learning curve is needed, in order to capitalize on the LCRO advantages [29]. Modular training enables the partitioning of the procedure in successive steps, each with its own optimization requirements[18]. The introduction of advanced LCRO courses, mentor guidance, and large operational volume exposure result in a considerable downgrade of the LC cut-off points[18,27]. These methods have been successfully enrolled in multiple national structured training programs, with promising results[17,26]. Nonetheless, surgeons in healthcare systems that have not included LCRO in their official guidelines, do not have access to similar training modules[22]. Therefore, the implementation of LCRO in such settings is based on the individual training efforts of the involved surgeons, with questionable, though, results.

In this study, we analyzed the pooled learning curve of two senior colorectal surgeons. LCRO training was not structured and included course attendance and proctor guidance. Despite this, previous experience in laparoscopic surgery and open colorectal resections could have impacted the pooled LCRO LC turning points. Therefore, our results may not reflect the typical LC pattern of an average surgical trainee.

Several limitations should be acknowledged, prior to the appraisal of our findings. First, despite the statistical significance of several LC turning points, our study incorporated a relatively small sample size. This prohibited further explanatory analyses, including risk-adjustment of the learning curves. Moreover, the innate discrepancy in terms of patient and surgical characteristics, degraded the significance of our results. Furthermore, another major source of bias could be the retrospective design of our study. Finally, the fact that only two consultants were included in this study, prohibited the safe extrapolation of these findings to a wider pool of colorectal surgeons and surgical trainees.

CONCLUSION

Overall, our study reported that the LCRO operation duration learning curve consists of three distinct phases. CPA estimated that the 110th case is the cut-off point between the first two phases. Stabilization of operative time is achieved after the 145th case. LCO and LRO subgroup analysis estimated the 58th and 52nd case as the respective turning points. In contrast to the open conversion and morbidity outcomes, a learning curve pattern was confirmed in pathology endpoints. The learning curves in our settings validate the comparability of the results, despite the absence of National or Surgical Society driven training programs. However, the initiation of a formal LCRO training policy is necessary for the safe and efficient implementation of these procedures.



DOI: 10.4253/wjge.v14.i6.387

Figure 1 Cumulative sum analysis of operation duration in laparoscopic colorectal operations. CUSUM: Cumulative sum; LCRO: Laparoscopic colorectal operations.

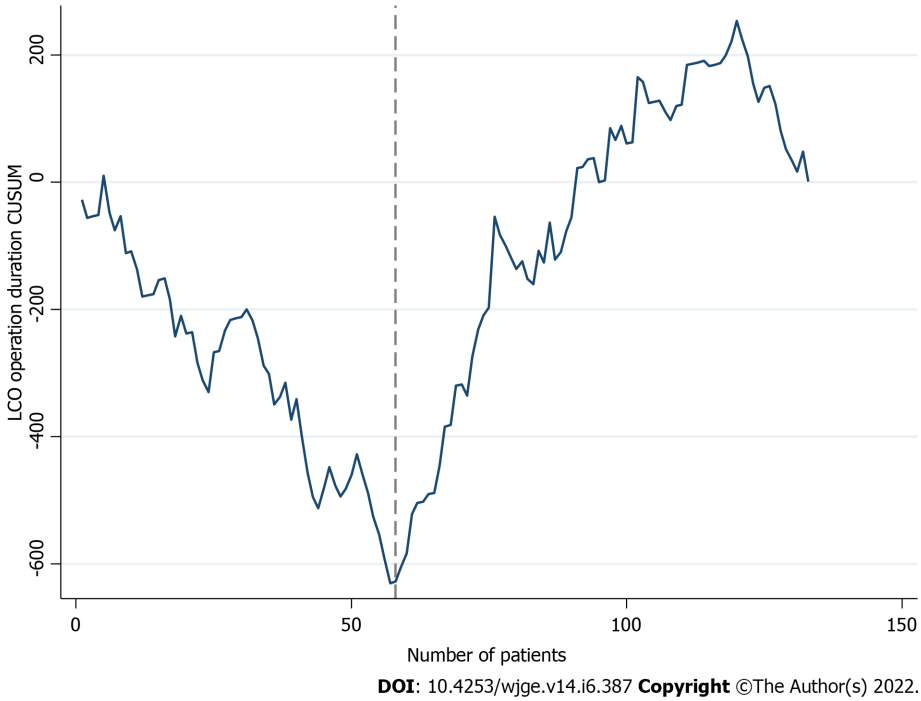


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Figure 2 Cumulative sum analysis of operation duration in laparoscopic colon operations. CUSUM: Cumulative sum; LCO: Laparoscopic colon operations.

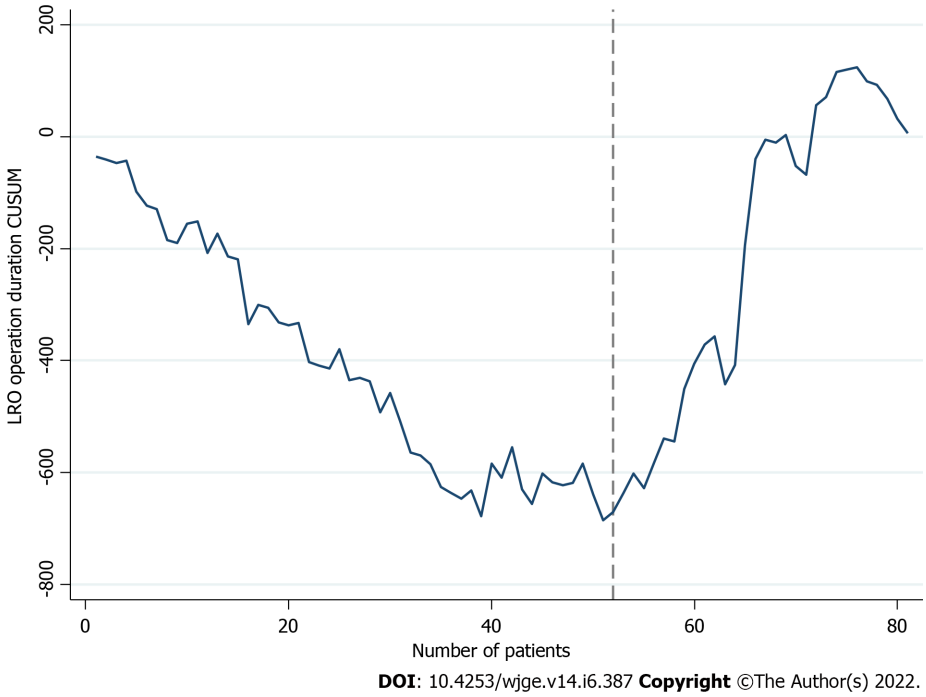

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Figure 3 Cumulative sum analysis of operation duration in laparoscopic rectal operations. CUSUM: Cumulative sum; LRO: Laparoscopic rectal operations.

ARTICLE HIGHLIGHTS

Research background

The introduction of structured training programs results in an enhanced learning process in laparoscopic colorectal surgery.

Research motivation

National training programs are not widely available, thus constraining the efficient adaptation of minimal invasive techniques in colorectal surgery.

Research objectives

To analyze the learning curve patterns in laparoscopic colorectal operations under a non-structured training setting.

Research methods

A retrospective analysis of a prospectively collected database was performed. Cumulative sum analysis and change point analysis were introduced for the evaluation of learning curve patterns.

Research results

In terms of operation duration, three learning curve phases were identified. A learning curve pattern was also confirmed in pathology endpoints, but not in the open conversion and complications outcomes.

Research conclusions

Laparoscopic colorectal operations under a non-structured training setting result in similar learning patterns with the respective structured training curves.

Research perspectives

The introduction of formal training programs in laparoscopic colorectal surgery is necessary for the safer and wider adoption of these techniques.

FOOTNOTES

Author contributions: Perivoliotis K, Baloyiannis I, and Tzovaras G designed the research study; Mamaloudis I, Volakakis G, and Valaroutsos A acquired the study data; Perivoliotis K and Baloyiannis I drafted the manuscript; Baloyiannis I and Tzovaras G critically revised and approved the final manuscript.

Institutional review board statement: This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. We consulted extensively with the IRB of University Hospital of Larissa who determined that our study did not need ethical approval since all procedures being performed were part of the routine care.

Informed consent statement: Informed consent was obtained from all individual participants included in the study.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: The datasets generated during the current study are available from the corresponding author on reasonable request.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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ORIGINAL ARTICLE

Observational Study

Role of endoscopic ultrasound and cyst fluid tumor markers in diagnosis of pancreatic cystic lesions

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Abstract

BACKGROUND

Pancreatic cystic lesions (PCLs) are common in clinical practice. The accurate classification and diagnosis of these lesions are crucial to avoid unnecessary treatment of benign lesions and missed opportunities for early treatment of potentially malignant lesions.

AIM

To evaluate the role of cyst fluid analysis of different tumor markers such as cancer antigens [*e.g.*, cancer antigen (CA)19-9, CA72-4], carcinoembryonic antigen (CEA), serine protease inhibitor Kazal-type 1 (SPINK1), interleukin 1 beta (IL1-β), vascular endothelial growth factor A (VEGF-A), and prostaglandin E2 (PGE2)], amylase, and mucin stain in diagnosing pancreatic cysts and differentiating malignant from benign lesions.

METHODS

This study included 76 patients diagnosed with PCLs using different imaging modalities. All patients underwent endoscopic ultrasound (EUS) and EUS-fine needle aspiration (EUS-FNA) for characterization and sampling of different PCLs.

RESULTS

The mean age of studied patients was 47.4 ± 11.4 years, with a slight female predominance (59.2%). Mucin stain showed high statistical significance in predicting malignancy with a sensitivity of 87.1% and specificity of 95.56%. It also showed a positive predictive value and negative predictive value of 93.1% and 91.49%, respectively ($P < 0.001$). We found that positive mucin stain, cyst fluid glucose, SPINK1, amylase, and CEA levels had high statistical significance ($P < 0.0001$). In contrast, IL-1β, CA 72-4, VEGF-A, VEGFR2, and PGE2 did not show any statistical significance. Univariate regression analysis for prediction of malignancy in PCLs showed a statistically significant positive correlation with mural nodules, lymph nodes, cyst diameter, mucin stain, and cyst fluid CEA. Meanwhile, logistic multivariable regression analysis proved that mural nodules, mucin stain, and SPINK1 were independent predictors of malignancy in cystic pancreatic lesions.

CONCLUSION

EUS examination of cyst morphology with cytopathological analysis and cyst fluid analysis could improve the differentiation between malignant and benign pancreatic cysts. Also, CEA, glucose, and SPINK1 could be used as promising markers to predict malignant pancreatic cysts.

Key Words: Pancreatic cystic neoplasm; Mucinous cystic neoplasm; Intraductal papillary mucinous neoplasm; Mucin stain; Amylase

Core Tip: Nowadays, the awareness of pancreatic cystic lesions has become an essential issue, especially with the increased incidence of asymptomatic pancreatic cysts in the general population. Therefore, the proper diagnosis, meticulous differentiation, and staging of these pancreatic cystic lesions are crucial for proper management and avoiding unnecessary treatment of benign lesions and missing early treatment of the malignant/pre-malignant lesions. Endoscopic ultrasound examination of cyst morphology with cytopathological and chemical analysis and cyst fluid analysis could improve the diagnostic capability. Also, many developed markers are valuable for predicting a malignant pancreatic cyst.

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INTRODUCTION

Pancreatic cystic lesions (PCLs) are not rare; they vary from a simple benign cyst to a highly malignant one[1]. Awareness of these lesions has increased in recent years, especially with the increased incidence of asymptomatic pancreatic cysts in the general population primarily due to improved detection by different advanced imaging modalities[2,3]. Therefore, the proper diagnosis, meticulous differentiation, and staging of these PCLs are crucial for proper management and avoiding unnecessary treatment of benign lesions and missing early treatment of the malignant/pre-malignant lesions[4,5].

Endoscopic ultrasound (EUS) has become an indispensable tool for diagnosing many pancreatic lesions; it has a benefit for better evaluation of number, location, dimensions, wall thickness, and the content of pancreatic cysts. Also, it is crucial in distinguishing the internal septae and solid areas within the cysts[6].

The morphological features of PCLs are not independent factors in differentiating malignant from nonmalignant lesions. The combination of both EUS-fine needle aspiration (EUS-FNA) findings with cystic fluid tumor marker analysis, along with clinical, radiologic, histologic, genetic, and molecular characteristics, enhances the diagnostic accuracy for PCLs and helps to construct a novel model in the era of PCL diagnosis[4].

Currently, many tumor markers, both in the serum and in pancreatic cyst fluid (CF), have been widely studied as a tool for distinguishing mucinous/malignant and non-mucinous pancreatic cystic lesions, such as carcinoembryonic antigen (CEA), cancer antigen (CA)19-9, CA125, CA15-3, and CA72-4 [7].

MATERIALS AND METHODS

Study design and aims

In this single tertiary referral center prospective study, the samples were collected and stored, and then all markers were detected in the same specimens in the same time. The study aimed primarily to evaluate the role of cyst fluid amylase and tumor markers such as CA 19-9, CEA, serine protease inhibitor Kazal-type 1 (SPINK1), IL1-β, CA 72-4, vascular endothelial growth factor A (VEGF-A), and prostaglandin E2 (PGE2) in addition to mucin stain in diagnosing pancreatic cysts and differentiating malignant from benign lesions.

Patients and recruitment

This prospective study was conducted on 76 patients diagnosed with PCLs using different imaging modalities such as computed tomography (CT), EUS, abdominal ultrasound, or magnetic resonance imaging (MRI). The candidates were recruited over 3 years from the Gastroenterology, Endoscopy, and Hepatology Unit, Internal Medicine Department, Kasr Al-Ainy, Cairo University. Fluid analysis was performed for CA 19-9, CA 72-4, CEA, VEGF-1, SPINK-1, IL1-b, PGE2, amylase, mucin stain, and cytopathology. We compared these data with the final diagnosis based on histopathology after surgical resection, positive cytopathology (positive for malignancy), and a long period of follow-up of the patients for at least 18 mo.

All patients underwent EUS examination for cyst characterization and sampling of the cystic lesions. All included patients were above 18 years of age. Patients included in this study were diagnosed with

large pancreatic cysts (larger than 3 cm), suspicious intraductal papillary mucinous neoplasm (IPMN), or pancreatic duct dilatation proved by magnetic resonance cholangiopancreatography. However, patients with small cysts (less than 1 cm), calculous cholecystitis, a potential risk for anesthesia, or a bleeding tendency (international normalized ratio > 1.5, or severe thrombocytopenia, with platelet count < 50000/mm^3) and patients who refused to participate were excluded from the study. Also, those who missed the follow-up were ruled out from the study. Our institution's Research Ethical Committee approved the study, and all patients gave their informed written consent before inclusion in the study, according to the ethical guidelines of the 1975 Declaration of Helsinki.

Examination procedure

All the patients, after thorough full history taking and clinical examination, were subjected to: (1) EUS examination using a linear Echoendoscope PENTAX EG3870UTK (HOYA Corporation, PENTAX Life Care Division, Showanomori Technology Center, Tokyo, Japan) connected to an ultrasound unit Hitachi AVIUS machine (Hitachi Medical Systems, Tokyo, Japan). All examinations were performed under deep sedation with IV propofol. For EUS-FNA, we used the Cook 19G and 22G needles (Echotip; Wilson-Cook, Winston Salem, NC). Prophylactic ceftriaxone (1 gm) was administered before the procedure; (2) characterization of the PCLs. All the characteristics of the PCLs were documented, including localization, number, dimensions, wall thickness, presence of septations or mural nodules, calcification, lymph nodes, and cystic dilatation of the main pancreatic duct. The color, transparency, and viscosity of the CF were also recorded; and (3) evacuation of the cystic fluid entirely with a single needle pass. Aspirated material inside the needle was spread over dry slides. Also, a proportion of the fluid sample (at least 2 mL) was sent for cytopathological examination, including mucin staining using alcian blue stain. At least 5 mL of cyst fluid was analyzed for CEA, SPINK1, IL1-β, CA 72-4, VEGF-A, PGE2, and CA-19-9 using two-site immunoassays (Beckman Coulter). Amylase was measured by the enzymatic colorimetric assay on a modular system (Roche).

Cysts were considered malignant when any of the following is present: (1) Cytopathological detection of malignancy; (2) presence of metastasis in the absence of other concomitant malignancies; (3) presence of mural nodules that progress in size within 6 mo; and (4) postoperative pathological diagnosis of malignancy if available. Cysts were considered benign when proved negative for malignancy by cytopathological examination and follow-up for 18 mo without increasing its size, the appearance of mural nodules or metastasis, or occurrence of obstructive jaundice.

The overall complication rate of EUS-FNA in the prospective series ranges from 0% to 2.5%[8]. Such complications include pain, infection, bleeding, acute pancreatitis, perforation of the esophagus or duodenum, bile peritonitis, and seeding of tumorous cells along the needle track[9]. Therefore, a prophylactic antibiotic in the form of 1 gm IM or slow IV third-generation cephalosporin was administered 6 h before the procedure. No major complications occurred in our series. However, self-limiting intracystic bleeding occurred in one patient, and mild pain occurred in three patients. All patients were discharged on the same day, and no hospital admission was needed.

Statistical analysis

Data management and analysis were performed using Statistical Package for Social Sciences v. 25. Numerical data are summarized using the mean and standard deviation, median, or range, as appropriate. Categorical data are summarized as numbers and percentages. Estimates of the frequency were calculated using the numbers and percentages. Numerical data were explored for normality using the Kolmogorov-Smirnov test and the Shapiro-Wilk test. To measure the association between variables: (1) Chi-square or Fisher's tests were used to compare independent groups concerning categorical data; (2) kappa statistics were computed to test the agreement between categorical variables. Their values ranged from zero to one; (3) the Mann-Whitney *U* test implemented comparisons between two groups for non-normally distributed numeric variables; and (4) *P* value ≤ 0.05 was considered significant.

RESULTS

This study included 76 patients [31 males (40.8%) and 45 females (59.2%)] with a mean age of 47.4 ± 11.4 years (Table 1).

EUS evaluation showed that most patients had a unilocular cyst (40 patients, 52.6%), while 36 patients (47.4%) had a multilocular cyst. Mural nodules were found in 24 patients (31.6%). In addition, most cysts had thin walls (77.6%) and clear contents (78.9%). Calcifications and lymph nodes were not found in 92.1% and 82.9% of patients, respectively. The pancreatic duct was dilated in 10 patients (13.2%) (Table 2).

Pancreatic cysts were diagnosed as being malignant/potentially malignant or benign in 38.2% and 61.8% of patients, respectively. Malignant cysts included mucinous cystadenocarcinoma (14.5%) (Figure 1A) and pancreatic adenocarcinoma (5.3%). On the other hand, potentially malignant cysts included IPMN with low (7.9%) and high-grade dysplasia (13.2%) and mucinous cystadenoma. Benign cysts included serous and mucinous cystic neoplasms (17.1%), pseudocysts (39.5%) (Figure 1B), and

Table 1 Descriptive data of included patients

Gender	Number	Percent (%)
Male	31	40.80%
Female	45	59.20%
Total	76	100%

Table 2 Endoscopic ultrasound findings of studied patients

EUS finding		Number	Percent (%)
Loculation	Unilocular	40	0.526
	Multilocular	36	0.474
Mural nodules	No	52	0.684
	Yes	24	0.316
Wall	Thin Wall	59	0.776
	Thick Wall	17	0.224
Content	Clear	60	0.789
	Turbid	16	0.211
Calcification	No	70	0.921
	Yes	6	0.079
LNs	No	63	0.829
	Yes	13	0.171
Pancreatic duct dilation	No	66	0.868
	Yes	10	0.132

EUS: Endoscopic ultrasound.

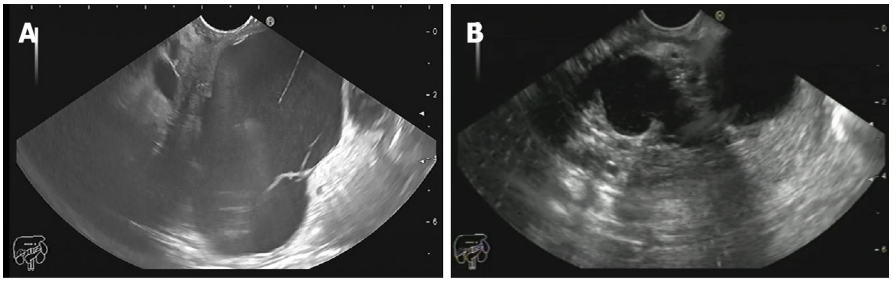

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Figure 1 Pancreatic body mucinous cystadenoma. A: Pancreatic body mucinous cystadenoma; B: Bilocular inflammatory pseudocyst in the gastric body.

cystic lymphangioma (1.3%) (Table 3).

Evaluating PCLs using mucin stain to differentiate between mucinous and non-mucinous pancreatic cystic lesions showed a sensitivity of 100%, specificity of 94%, and accuracy of 96.04% (Table 4). Also, we found that there was high statistical significance for mucin stain in predicting malignancies with a sensitivity of 87.1%, specificity of 95.56%, positive predictive value (PPV) of 93.1%, and negative predictive value (NPV) of 91.49% (P value < 0.001) (Table 5).

The median CF CEA level was 90 (8.39- 2750) ng/mL. Also, the median CF SPINK1 level was 0.56 (0.35-0.97) ng/mL, and the median CF glucose level was 50 mg/dL (Table 6). When we categorized the CF level of CEA above and below 192 ng/mL, the malignant/potentially malignant cysts were more likely to have a CEA level above 192 ng/mL (P = 0.001), as shown in Table 7.

As shown in Table 6, CF CEA level and CF amylase were significantly higher in malignant/potentially malignant cysts than in benign cysts with a median of 15.8 *vs* 6.4 and 130.5 *vs* 3060 (P = 0.004

Table 3 Final diagnosis

Final diagnosis	Number	Percent (%)
Pancreatic pseudocyst	30	39.5
Pancreatic pseudocyst with WOPN	1	1.3
Serous cystadenoma	13	17.1
Mucinous cystadenoma	11	14.5
IPMN (high grade dysplasia)	10	13.2
IPMN (low grade dysplasia)	6	7.9
Pancreatic adenocarcinoma	4	5.3
Cystic lymphangioma	1	1.3
Total	76	100

IPMN: Intraductal papillary mucinous neoplasm; WOPN: Walled-off pancreatic necrosis.

Table 4 Mucin stain in detecting mucinous from non-mucinous pancreatic cystic lesions

Statistic	Value	95%CI
Sensitivity	100%	86.77% to 100%
Specificity	94%	83.45% to 98.75%
Positive likelihood ratio	16.67	5.56 to 49.93
Negative likelihood ratio	0	
Disease prevalence	34.21%	23.71% to 45.99%
Positive predictive value	89.66%	74.31% to 96.29%
Negative predictive value	100%	
Accuracy	96.05%	88.89% to 99.18%

Table 5 Mucin stain in detecting benign from malignant pancreatic cystic lesions

Statistic	Value	95%CI
Sensitivity	87.10%	70.17% to 96.37%
Specificity	95.56%	84.85% to 99.46%
Positive likelihood ratio	19.60	5.02 to 76.47
Negative likelihood ratio	0.14	0.05 to 0.34
Disease prevalence	40.79%	29.65% to 52.67%
Positive predictive value	93.10%	77.58% to 98.14%
Negative predictive value	91.49%	81.12% to 96.41%
Accuracy	92.11%	83.60% to 97.05%

and 0.034, respectively). Also, CF amylase and CF CEA showed statistical significance in predicting malignancy (P = 0.028 and < 0.001, respectively). Furthermore, the SPINK1 level in CF was significantly higher in malignant/potentially malignant cysts compared to benign ones (0.91 *vs* 0.47, P = 0.001). Meanwhile, glucose was markedly consumed in malignant/potentially malignant cysts than in benign cysts (21.5 *vs* 68.5, P = 0.0001) (Table 7).

Comparing different CF markers in predicting malignant PCLs among the studied patients revealed that positive Mucin stain, CF glucose, SPINK1, amylase, and CEA showed high statistical significance (P < 0.0001, 0.0001, 0.001, 0.034, and 0.004, respectively). However, IL1-β, CA 72-4, VEGF-A, VEGFR2, and PGE2 did not show any statistical significance (Table 8).

Table 6 Cyst fluid carcinoembryonic antigen, serine protease inhibitor Kazal-type 1, and glucose level in studied patients

Biochemical test	Median (IQR)	Range
CEA (ng/ml)	90 (8.78- 1560)	(5-100000)
SPINK1 (ng/ml)	0.56 (0.35-0.97)	(0.1-2.32)
Glucose (mg/dl)	50 (10-84)	(2-171)

IQR: Interquartile range.

Table 7 Cystic fluid analysis of malignant/potentially and benign cysts

Variable	Benign group(n = 45)	Malignant group(n = 31)	P value
Mucin stain positivity	2 (4.4%)	27 (87.1%)	< 0.0001
Number (%)			
Glucose (mg/dl)	21.5 (4-45)	68.5 (47-87)	0.0001
median (IQR)			
IL1b (pg/mL)	0.37 (0.58)	0.34 (0.45)	0.845
(median, IQR)			
CA 72-4 (U/mL)	6.36 (9.7)	7.4 (7.6)	0.323
(median, IQR)			
VEGF-A (pg/ml)	707.8 (1056)	736.9 (2262)	0.866
(median, IQR)			
VEGFR2 (pg/ml)	2.5 (5.3)	1.3 (3)	0.281
(median, IQR)			
SPINK1 (ng/ml)	0.91 (0.41-1.45)	0.47 (0.3-0.72)	0.001
median (IQR)			
PGE2 (pg/ml)	307.2 (131)	409.7 (176)	0.121
(median, IQR)			
CF amylase (U/L)	130.5 (353)	3060 (5191)	0.034
(median, IQR)			
CF CEA (ng/ml)	6.4 (234)	15.8 (2532)	0.004
(median, IQR)			
CEA (> 192 ng/mL)	15	5	0.001

CEA: Carcinoembryonic antigen; CF: Cyst fluid; IQR: Interquartile range; VEGFR2: Vascular endothelial growth factor receptor 2; SPINK1: Serine protease inhibitor Kazal-type 1.

Univariate regression analysis showed a statistically significant association between malignancy in PCLs and mural nodules, lymph nodes, cyst diameter, mucin stain, CF CEA, SPINK1, and CEA level > 192 ng/mL. In comparison, multivariable regression analysis proved that mural nodules, mucin stain, SPINK1, and CEA level > 192 ng/mL were independent predictors of malignancy in cystic pancreatic lesions (Table 9).

Receiver operating characteristic (ROC) curves were constructed to assess the diagnostic accuracy of CF CEA, SPINK1, IL1-β, CA 72-4, VEGF-A, PGE2, and CA-19-9 in predicting malignant cysts. It revealed that the area under the curve was comparable for CEA, glucose, and SPINK1 (0.75, 0.76, and 0.72, respectively) (Figures 2A-C).

The sensitivity of EUS diagnosis in detecting malignant and premalignant pancreatic cysts was 66.7%, while 69.2% for the specificity, 60% PPV, and 75% NPV with an overall accuracy of 68.2% (Table 10).

Out of 76 patients, two patients died. Both patients had pancreatic adenocarcinoma. Most of the patients showed a stationary course (40 patients, 52.6%), and only three patients (3.9%) ran a regressive

Table 8 Value of different variables in predicting malignancy

Variable	Criterion	Specificity	Sensitivity	PPV	NPV	*P* value	AUC
Age	> 35	0.244	1	0.4745	1	0.605	0.534
Mucin stain		0.9556	0.871	0.931	0.9149	< 0.001	0.913
Glucose (mg/dL)	≤ 42	0.7353	0.8478				0.76
IL1b (pg/mL)	< 1.13	0.209	0.9	0.4363	0.7464	0.761	0.521
CA 72-4 (U/mL)	> 4.3138	0.467	0.677	0.4657	0.678	0.32	0.567
VEGF-A (pg/mL)	> 1221.7	0.844	0.29	0.561	0.634	0.87	0.511
VEGFR2 (pg/ml)	> 6.601	0.933	0.29	0.7482	0.657	0.301	0.573
SPINK1 (μg/L)	≥ 0.58	0.6533	0.7059	0.708	0.623		0.72
PGE2 (pg/ml)	> 311.77	0.556	0.8	0.5529	0.802	0.102	0.683
CF amylase (U/L)	> 270	0.71	0.711	0.629	0.781	0.028	0.644
CF CEA (ng/ml)	> 8	0.742	0.689	0.622	0.795	< 0.001	0.761

CA: Cancer antigen; CF: Cyst fluid; VEGFR2: Vascular endothelial growth factor receptor 2; PPV: Positive predictive value; NPV: Negative predictive value.

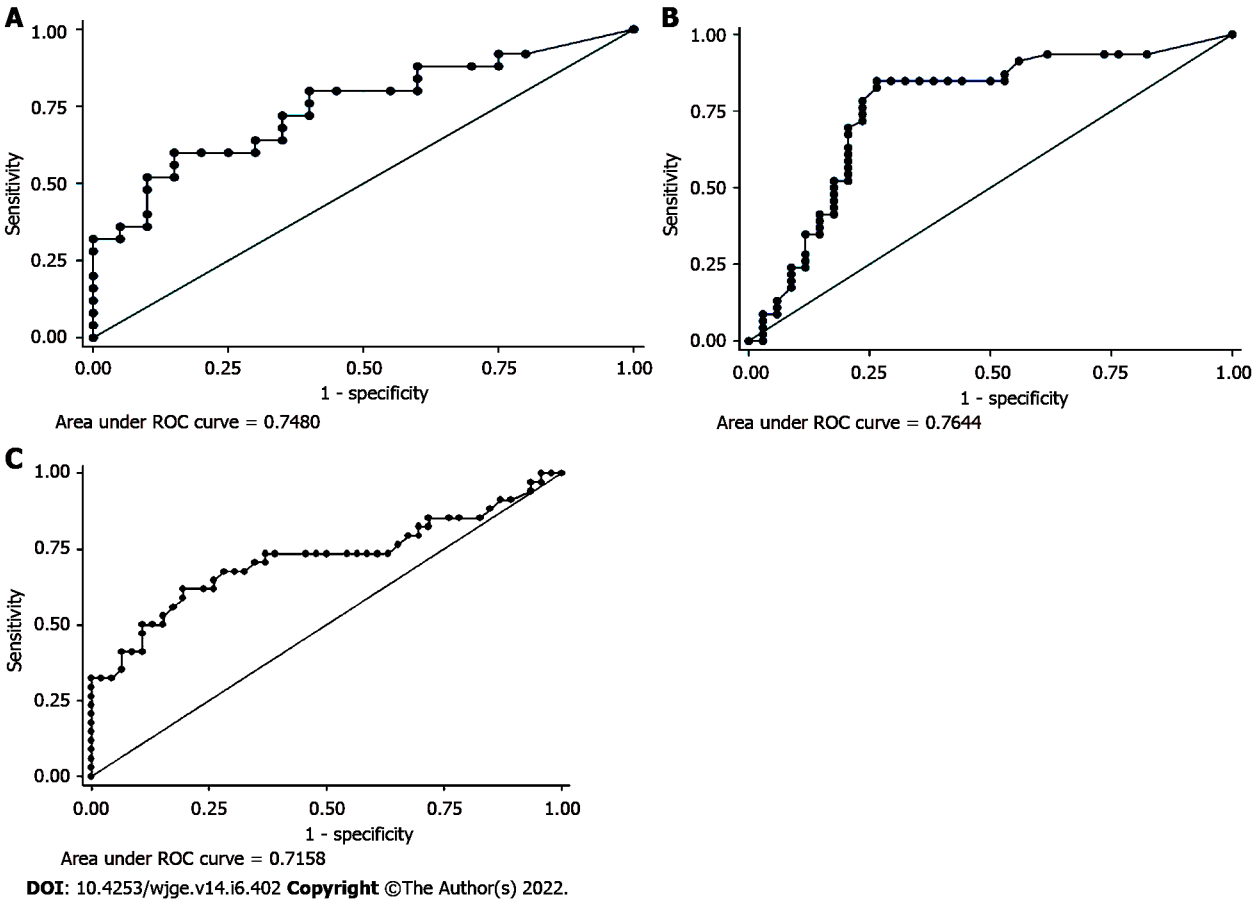

Figure 2 Receiver operating characteristic curve analysis. A: Cyst fluid carcinoembryonic antigen level; B: Glucose level in cyst fluid; C: Cyst fluid serine protease inhibitor Kazal-type 1 level. ROC: Receiver operating characteristic.

course, as demonstrated in Table 11. Two patients with inflammatory pseudocyst underwent a percutaneous pig-tail insertion; one of them was complicated by abscess formation and proceeded to surgery. Most of the patients required no intervention (56 patients, 73.7%). However, some patients were referred to surgeries (17 patients, 22.4%), and only one patient underwent cystogastrostomy, as demonstrated in Table 12.

Table 9 Logistic regression analysis for predictors of malignancy in cystic pancreatic lesions

Variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age	1.06 (0.97-1.06)	0.4312		
Mural nodules	6.6 (2.3- 19.3)	0.0006	5.7 (1.37-24.6)	0.0172
Wall thickness	1.39 (0.47-4.124)	0.5514		
LNs	11.82 (2.4-58.4)	0.0024	0.14 (0.006-3.3)	0.2219
Content	0.59 (0.18-1.923)	0.3851		
Loculation	1.1 (0.43-2.68)	0.8826		
Calcification	1.5 (0.28-7.97)	0.6342		
Shortest Diameter	0.965 (0.94-0.99)	0.0189	1.06 (0.92-1.22)	0.4044
Longest Diameter	0.971(0.95-0.99)	0.0112	0.913 (0.81- 1.03)	0.1326
Mucin Stain	145 (24.8-847.2)	< 0.0001	82.4 (12.1-561)	< 0.0001
Glucose	0.97 (0.96-0.99)	> 0.001	0.99 (0.97-1.01)	0.48
IL1b (pg/mL)	0.91 (0.702-1.18)	0.496		
CA 72-4	1.02 (0.98-1.053)	0.3017		
VEGF-A	1.0001(0.99-1.0005)	0.5782		
VEGFR2	1.14 (0.99-1.318)	0.0782		
SPINK1	9.09 (2.62-31.59)	0.001	23.65 (3.10-180.62)	0.002
PGE2 (pg/mL)	1.01 (0.999-1.02)	0.0798		
CF Amylase	1 (1-1)	0.8593		
CF CEA	1.0003 (1.0001-1.0005)	0.0152	1.0001 (0.99-1.0006)	0.5978
CEA > 192 (ng/mL)	6.47 (2.05-20.42)	0.001	14.12 (2.39-83.22)	0.003

OR: Odds ratio; CI: Confidence interval; LNs: Lymph-nodes; CF: Cyst fluid; CA: Cancer antigen; CEA: Carcinoembryonic antigen; SPINK1: Serine protease inhibitor Kazal-type 1; IL1-β: Interleukin 1 beta; CA 72-4: Human cancer antigen 72-4; VEGF-A: Vascular endothelial growth factor A; VEGFR2: Vascular endothelial growth factor receptor 2, PGE2: Prostaglandin E2.

Table 10 Performance of EUS diagnosis for malignant/premalignant and benign cysts

Statistic	Value	95%CI
Sensitivity	0.6667	40.99% to 86.66%
Specificity	0.6923	48.21% to 85.67%
Positive predictive value	0.6	43.60% to 74.42%
Negative predictive value	0.75	59.79% to 85.82%
Accuracy	0.6818	52.42% to 81.39%

DISCUSSION

There are great challenges in diagnosing and managing PCLs that have become a common problem faced by many physicians and surgeons[10]. Some PCLs have a malignant potential with a significant risk of developing invasive cancer[11]. Therefore, the accurate classification and diagnosis of pancreatic cysts provide a potential for preventing and early detection of pancreatic cancer. On the other hand, misdiagnosis or unnecessary surgeries may lead to high cost and harm to the patients[10].

Unfortunately, imaging modalities such as CT and MRI have insufficient sensitivity and specificity to characterize PCLs and provide a suboptimal classification and diagnosis due to poor interobserver variability[12].

Table 11 Follow-up data of studied patients

Follow-up	Stationary	Regressive	No-recurrence	Progressive	Died
Pancreatic pseudocyst (n = 30)	27 (35.5%)	3 (3.9%)	0	0	0
Pancreatic pseudocyst with WOPN (n = 1)	0	0	1 (1.3%)	0	0
Serous cystadenoma (n = 13)	12 (15.7%)	0	1 (1.3%)	0	0
Mucinous cystadenoma (n = 10)	9	0	1 (1.3%)	0	0
Mucinous cystadenocarcinoma (n = 1)	0	0	0	1	0
IPMN (high grade dysplasia) (n = 10)	3	0	7	0	0
IPMN (low grade dysplasia) (n = 6)	6	0	0	0	0
Pancreatic adenocarcinoma (n = 4)	0	0	2 (2.6%)	0	2 (2.6%)
Cystic lymphangioma (n = 1)	1 (1.3%)	0	0	0	0
Total (n = 76)	40 (52.6%)	3 (3.9%)	5 (6.5%)	0	2 (2.6%)

Table 12 Intervention required for studied patients

Intervention required	No	Surgery	Pig-tail drainage	Cysto-gastrostomy
Pancreatic pseudocyst (n = 30)	26 (34.2%)	1 (1.3%)	2 (2.6%)	1 (1.3%)
Pancreatic pseudocyst with WOPN (n = 1)	0	1 (1.3%)	0	0
Serous cystadenoma (n = 13)	12 (15.8%)	1 (1.3%)	0	0
Mucinous cystadenoma (n = 10)	9 (11.7%)	1 (1.3%)	0	0
Mucinous cystadenocarcinoma (n = 1)	1 (1.3%)	0	0	0
IPMN (high grade dysplasia) (n = 10)	1 (1.3%)	9 (11.8%)	0	0
IPMN (low grade dysplasia) (n = 6)	6 (7.9%)	0	0	0
Pancreatic adenocarcinoma (n = 4)	0	4 (5.2%)	0	0
Cystic lymphangioma (n = 1)	1 (1.3%)	0	0	0
Total (n = 76)	56 (73.7%)	17 (22.4%)	2 (2.6%)	1 (1.3%)

EUS is considered the most sensitive tool in delineating the pancreatic cyst characteristics with the capacity to identify the presence of mural nodules and solid components[13]. Also, it has a benefit in enabling EUS-FNA for cytology[14]. Nonetheless, cytology still has a limited diagnostic yield with a pooled sensitivity of 63% and specificity of 88%[15].

Owing to the limited diagnostic accuracy for different pancreatic cysts with the current diagnostic modalities, analysis of the pancreatic CF obtained *via* EUS-FNA could improve the diagnostic accuracy for pancreatic cysts and help determine the malignant potentiality. Therefore, there is still a growing research interest in discovering and validating novel CF biomarkers that may improve diagnostic accuracy. The present study was designed to determine the role of CF amylase and tumor markers such as CA 19-9, CEA, SPINK1, IL1-β, CA 72-4, VEGF-A, and PGE2 in addition to mucin stain in diagnosing pancreatic cysts and differentiating malignant from benign lesions.

The presence of solid components inside the cyst on imaging could be a significant predictor of malignancy, as reported in many studies[16-18]. Also, we found that the presence of mural nodules was highly predictive of malignancy in univariate and multivariate logistic regression analysis (P = 0.0006 and 0.0172, respectively) along with cyst diameter (P = 0.0189 for shortest diameter and 0.0112 for longest diameter) and lymph node enlargement (P = 0.0024).

In a study conducted by Okasha *et al*[19] analyzing the CF amylase of 44 patients, they concluded that pancreatic CF amylase level could differentiate between malignant/potentially malignant and benign cysts with a sensitivity of 58%, specificity of 75%, PPV of 73%, NPV of 60%, and accuracy of 66%.

In our study, CF CEA level and CF amylase were significantly higher in malignant/potentially malignant cysts than in benign cysts (P = 0.004 and 0.034, respectively). This finding agrees with other studies stating that pancreatic CF CEA offers the best diagnostic performance than any other single test, especially in differentiating mucinous and non-mucinous cysts[20].

A large multi-institutional study conducted on 1861 patients reported that CEA > 192 ng/mL could differentiate mucinous from non-mucinous cysts with an accuracy of 77%[21]. Their findings are in

concordance with our study that reported that the malignant/potentially malignant cysts had CEA levels above 192 ng/mL ($P = 0.001$).

In CF, positive mucin stain was significantly more frequent in malignant cysts (87.1%) ($P < 0.0001$). Twenty-seven cysts were positive for mucin stain, with a sensitivity of 87.1% and specificity of 95.56% in differentiating benign from malignant PCLS. Also, mucin staining differentiates mucinous from non-mucinous cysts with a sensitivity and specificity of 100% and 94%, respectively. The results in the current study were more compatible with an Egyptian study by Okasha and his colleagues. They showed that pancreatic CF positive mucin stain was 85% sensitive and 95% specific in detecting mucinous or non-mucinous pancreatic cysts with a 92% PPV, 91% NPV, and 91% accuracy. Also, positive mucin staining was 63% sensitive and 97% specific in differentiating malignant/potentially malignant from benign pancreatic cysts with a PPV of 96%, NPV of 72%, and overall accuracy of 80%. This outcome is in concordance with a recent study by Okasha and his colleagues that showed that a CF positive mucin stain has a sensitivity of 85.5% and specificity of 86.1% for detecting mucinous cystic neoplasm with a 72.3% PPV, 93.3% NPV, and 85.9% accuracy[4]. Many studies also reported that the mucin staining could be complementary to cyst CEA levels and cytology, and when one out of three was found to be positive, this increases the sensitivity to 92% and specificity to 52%, as in a study conducted by Morris-Stiff *et al*[22].

In our study, CF glucose was markedly consumed in malignant/potentially malignant cysts than in benign cysts (21.5 *vs* 68.5, $P = 0.0001$). Since glucose is a simple and cheap biomarker, it could be used as a marker for differentiation between benign and malignant pancreatic cysts with a relatively low cost [23-25].

In 2004, Raty *et al*[26] were the first to evaluate the role of CF SPINK1 in differentiating potentially malignant from benign cysts. They reported that the SPINK1 level was higher in malignant/potentially malignant than in benign cystic pancreatic lesions (1609 ± 418 *vs* 46 ± 21 ug/L; $P = 0.0001$). These findings matched our study that showed that SPINK1 level was higher in malignant/potentially malignant cysts than in benign ones (0.91 *vs* 0.47, $P = 0.001$) with a sensitivity and specificity of 70.59% and 65.33%, respectively (Table 8).

In our study, mural nodules, cyst diameter, lymph node enlargement, mucin stain, CF CEA, SPINK1, and glucose measurements in CF were highly predictive of malignancy in univariate analysis. In comparison, only mural nodules, mucin stain, and SPINK1 were highly predictive of malignancy in multivariate analysis.

Of all these markers measured in CF, CEA, glucose, and SPINK1 were independent predictors of malignancy, suggesting that these markers could help differentiate potentially malignant cysts from benign cysts.

The analysis of recent markers - not investigated in this study – such as CF DNA is recommended for future research because it might add more diagnostic value in differentiating benign from malignant cysts.

CONCLUSION

Conclusion

EUS examination of cyst morphology with cytopathological and chemical analysis and CF analysis could improve the differentiation between malignant and benign pancreatic cysts. Also, CEA, glucose, and SPINK1 are valuable markers for predicting a malignant pancreatic cyst.

Recommendations

Further studies addressing new markers are recommended, which will provide a panel of laboratory data to recognize the malignant and potentially malignant lesions to establish a standard protocol for diagnosis and management. Also, CF DNA is considered a potential diagnostic agent with particular possible use in differentiating between benign and malignant cysts. Further investigation regarding this biomarker is recommended.

ARTICLE HIGHLIGHTS

Research background

Nowadays, the awareness of pancreatic cystic lesions has become an essential issue, especially with the increased incidence of asymptomatic pancreatic cysts in the general population. Therefore, the proper diagnosis, meticulous differentiation, and staging of these pancreatic cystic lesions (PCLs) are crucial for proper management and avoiding unnecessary treatment of benign lesions and missing early treatment of the malignant/pre-malignant lesions. Endoscopic ultrasound (EUS) examination of cyst morphology with cytopathological and chemical analysis and cyst fluid analysis could improve the diagnostic capability. Also, many developed markers are valuable for predicting a malignant pancreatic cyst.

Research motivation

EUS examination of cyst morphology with cytopathological and chemical analysis and cyst fluid analysis could improve the differentiation between malignant and benign pancreatic cysts. Also, carcinoembryonic antigen (CEA), glucose, and the serine protease inhibitor Kazal-type 1 (SPINK1) are valuable markers for predicting a malignant pancreatic cyst.

Research objectives

To evaluate the role of cyst fluid analysis of different tumor markers such as cancer antigens (*e.g.*, CA19-9 and CA72-4), carcinoembryonic antigen (CEA), SPINK1, interleukin 1 beta (IL-1β), vascular endothelial growth factor A (VEGF-A), prostaglandin E2 (PGE2), amylase, and mucin stain in diagnosing pancreatic cysts and differentiating malignant from benign lesions.

Research methods

This study included 76 patients diagnosed with PCLs using different imaging modalities. All patients underwent EUS and EUS-FNA for characterization and sampling of different PCLs.

Research results

The mean age of studied patients was 47.4 ± 11.4 years, with a slight female predominance (59.2%). Mucin stain showed high statistical significance in predicting malignancy with a sensitivity of 87.1% and specificity of 95.56%. It also showed a positive predictive value and negative predictive value of 93.1% and 91.49%, respectively ($P < 0.001$). We found that positive mucin stain, cyst fluid glucose, SPINK1, amylase, and CEA levels had high statistical significance ($P < 0.0001$). In contrast, IL-1β, CA 72-4, VEGF-A, VEGFR2, and PGE2 did not show any statistical significance. Univariate regression analysis for prediction of malignancy in PCLs showed a statistically significant positive correlation with mural nodules, lymph nodes, cyst diameter, mucin stain, and cyst fluid CEA. Meanwhile, logistic multivariable regression analysis proved that mural nodules, mucin stain, and SPINK1 were independent predictors of malignancy in PCLs.

Research conclusions

EUS examination of cyst morphology with cytopathological analysis and cyst fluid analysis could improve the differentiation between malignant and benign pancreatic cysts. Also, CEA, glucose, and SPINK1 could be used as promising markers to predict malignant pancreatic cysts.

Research perspectives

Further studies addressing new markers are recommended, which will provide a panel of laboratory data to recognize the malignant and potentially malignant lesions to establish a standard protocol for diagnosis and management. Also, cyst fluid DNA is considered a potential diagnostic agent with particular possible use in differentiating between benign and malignant cysts. Further investigation regarding this biomarker is recommended.

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ORIGINAL ARTICLE

Retrospective Study

Safety of endoscopy in patients undergoing treatments with antiangiogenic agents: A 5-year retrospective review

Mohammad Azam, Amit Hudgi, Pearl Princess Uy, Jinal Makhija, John Erikson L Yap

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Abstract

BACKGROUND

Antiangiogenic agents (AAs) are increasingly used to treat malignant tumors and have been associated with gastrointestinal (GI) bleeding and perforation. Elective surgeries and endoscopy are recommended to be delayed for 31 d until after AAs treatment. Data regarding the safety of endoscopy while on antiangiogenic agents is extremely limited. No guidelines are in place to address the concern about withholding these anti-angiogenic drugs.

AIM

To evaluate the risks of endoscopy in patients on antiangiogenic agents from 2015 to 2020 at our institution.

METHODS

This is a single centered retrospective study approved by the institutional review board statement of the institution. Patients that underwent endoscopy within 28 d of antiangiogenic agents' treatment were included in the study. Primary outcome of interest was death, and secondary outcomes included perforation and GI bleeding. Data were analyzed utilizing descriptive statistics. Fifty-nine patients were included in the final analysis and a total of eighty-five procedures were performed that were characterized as low risk and high risk.

RESULTS

Among the 59 patients a total of 85 endoscopic procedures were performed with 24 (28.2%) categorized as high-risk and 61 (71.8%) procedures as low-risk. Of the

total number of patients, (50%) were on bevacizumab and the rest were on imatinib (11.7%), lenvatinib (6.7%) and, ramucirumab (5%). The average duration between administration of AAs and the performance of endoscopic procedures was 9.9 d. No procedure-related adverse events were noted among our study population. We did observe two deaths with one patient, on lenvatinib for metastatic hepatocellular carcinoma, who had persistent bleeding despite esophageal variceal banding and died 4 d later from hemorrhagic shock. Another patient was diagnosed with acute myeloid leukemia died 24 d after an esophagogastroduodenoscopy with biopsy after transition to comfort care.

CONCLUSION

As per this single center retrospective study, the rate of endoscopic procedure-related adverse events and death within 28 d of AA administration appears to be low.

Key Words: Antiangiogenics; Endoscopy; Bevacizumab; Lmatinib; Lenvatinib; Adverse events

Core Tip: This single centered study highlights low adverse events of anti-angiogenics after endoscopic procedures. Currently, the consensus recommends holding anti-angiogenics 28 d prior to the procedure. This small sample study sheds light on the need to hold anti-angiogenics prior to endoscopic procedure and affirms to not delay emergent endoscopic procedures.

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INTRODUCTION

Angiogenesis is a complex process of forming vascular network by endothelial cells proliferation mediated by growth factors like vascular endothelial growth factors (VEGF), insulin like growth factors, fibroblast growth factors and hypoxia inducible factors. It is first initiated during embryogenesis from mesodermal precursor cells, later repeated during process of healing. Similarly, when tumor cells are subjected to hypoxia, they produce growth factor leading to angiogenesis. This not only provide a source of nutrition but also a means for metastasis.

Folkman postulated the idea of antiangiogenic agents (AAs) as an effective cancer therapy in early 1970[1]. Currently, AAs are widely used in the treatment of malignant tumors owing to their effectiveness in increasing survival. Monoclonal antibodies, VEGF decoy receptor, and small molecule tyrosine kinase inhibitors are three major classes of anti-angiogenics currently in clinical practice[2]. However, VEGF also play a crucial role in wound healing and the use of AAs may potentially lead to complications such as bleeding and impaired wound healing[1,3].

Post-procedure adverse events were higher among patients receiving AAs[4]. The potential for increased occurrence of complications such as bleeding among cancer patients on AAs after procedures have led to the postponement of elective surgical procedures and endoscopies for at least 28 d after AA treatment. The mechanism of gastrointestinal (GI) perforation is attributed to splanchnic or mesenteric thrombi, impaired healing and proliferation, decreased blood supply to intestinal wall, and decreased stability secondary to tumor destruction have been postulated[5]. There is limited and inconsistent data in the literature regarding the rate of adverse events during endoscopy among patients on AAs. Imbulgoda *et al*[6] reported two complications of perforation (2/80 patients) in patient receiving bevacizumab while undergoing placement of self-expanding metal stent. More recently Kachaamy *et al*[7] revealed a low adverse event of 1.6% (7/455) in patients receiving AA. The cautious approach of delaying even low risk endoscopic procedures among patients receiving AAs may have resulted from the extrapolation of findings from studies of surgical procedures where increased adverse events like bleeding and impaired wound healing were observed[4]. It is important to note that endoscopic procedures are not as invasive as other surgical procedures and recommendations should not be solely based on data from surgical procedures.

In this single centered study, we reviewed medical records of the patients who underwent GI endoscopy after receiving anti-angiogenics therapy within the past 28 d. Here we aim to investigate 30 d adverse events in patients receiving AA undergoing an endoscopic procedure.

MATERIALS AND METHODS

Study design and patient population

This is a single center retrospective study conducted at a non-National Cancer Institute (NCI) designated hospital specializing in treatment of cancers in the state of Georgia, United States. Inclusion criteria for the study were: (1) Patients receiving treatment with AAs including vascular endothelial growth factor (VEGF), VEGF receptor inhibitors, epidermal growth factor receptor inhibitors, multi-targeted tyrosine kinase inhibitors, and mammalian target of rapamycin inhibitor; and (2) Patients undergoing endoscopic procedures within 28 d of AA administration between from January 1, 2015 - March 31, 2020. Exclusion criteria included: Age less than 18 years old. All patients undergoing endoscopic procedures within 28 d after administration of AAs were included in the study analysis. The Augusta University Investigation Review Boards approved this study.

Patients who met the inclusion and exclusion criteria were identified using I2B2 software, and details regarding the endoscopic procedures and the timing of AA administration were obtained from the electronic medical records. Endoscopic procedures were categorized as either high risk or low risk based on existing literature regarding endoscopic procedural risks associated with antithrombotic agents[8]. Low risk procedures included diagnostic endoscopies or with biopsy. In contrast, high risk procedures consisted of stent placements, gastrostomy tube placements, snare polypectomy, endoscopic retrograde cholangiopancreatography, and endoscopic ultrasound with fine needle aspiration.

Statistical analysis

Statistical analyses were performed utilizing simple descriptive statistics including percentages and frequencies. The demographic data, the mortality rate and the endoscopic adverse events were analyzed using descriptive statistics. The primary outcome measure was mortality rate within 30 d of endoscopy whereas the secondary outcome measures were procedure-related adverse events such as bleeding and perforation within 30 d of endoscopy. The adverse events were labeled according to the common terminology criteria for adverse events version (have version 5.0 now) which defines adverse events (AEs) as an unintended and unfavorable outcome associated with a medical treatment or procedure that may or may not be associated to the medical treatment or procedure. Classification of the severity of AEs were based on a grading system from 1 to 5 wherein 1 is mild, 2 is moderate, 3 is severe, 4 is life-threatening and 5 is death. The mortality rate and incident rate of AEs were determined using the total number of study participants as the denominator.

RESULTS

Patient characteristics

Fifty-nine patients (M/F = 25/34) were included in this study who underwent a total of 85 endoscopic procedures. The mean age of the study population was 64.9 years at the time of endoscopy. Majority of the patients were Caucasians (54.2%) or African Americans (40.7%). The most common malignancy types were colorectal cancer (20.7%), liver (11.9%), ovarian (10.2%) and lung (10.2%); and the majority (59.3%) had stage IV metastatic disease at the time of endoscopy (refer to Table 1). Thirty patients (50%) were on bevacizumab whereas other patients were on imatinib (11.7%), lenvatinib (6.7%), ramucirumab (5%) as detailed on Table 2. One of the patients with the diagnosis of acute myeloid leukemia (AML) who was being treated with two anti-angiogenic agents bevacizumab and sorafenib.

Procedures

A total of 85 endoscopic procedures were performed with 24 (28.2%) categorized as high-risk and 61 (71.8%) procedures as low-risk. High risk procedures included variceal bleeding control, percutaneous gastrostomy tube placement, pneumatic balloon dilation, and stent placement while low-risk included diagnostic procedures along with mucosal biopsies. The average duration between administration of AAs and the performance of endoscopic procedures was 9.9 d (Table 3).

Adverse events and mortality

Among the eighty-five endoscopic procedures that were performed, there were no procedure related adverse events that were documented. One patient on lenvatinib therapy for metastatic hepatocellular carcinoma had persistent bleeding despite esophageal variceal banding and died 4 d later from hemorrhagic shock. Another patient on sorafenib therapy for AML died 24 d after an esophago-gastroduodenoscopy with biopsy while on hospice care (Table 4).

Table 1 Baseline characteristics of patient population on anti-angiogenic agents

Characteristics	Anti-angiogenic agents (*n* = 59)
Age	64.9
Female	34 (57.62%)
Race	
Caucasian	32 (54.2%)
African American	24 (40.7%)
Hispanic	3 (5.1%)
Malignancy sites	
Colorectal cancer	12 (20.3%)
Hepatocellular cancer	7 (11.9%)
Ovarian cancer	6 (10.2%)
Lung	6 (10.2%)
CML/AML	5 8.5%)
Renal cell cancer	4 (6.8%)
Oropharyngeal cancer	3 (5.1%)
Uterine	2 (3.4%)
Pancreas	2 (3.4%)
Gastric cancer	2 (3.4%)
Fibrosarcoma	2 (3.4%)
Peritoneal carcinomatosis	2 (3.4%)
Cervical cancer	2 (3.4%)
Fallopian tube	1 (1.7%)
Breast cancer	1 (1.7%)
Other	2 (3.4%)
HHT/Hereditary eosinophilia	
Stage of malignancy	
Unstageable	9 (13.6%)
Stage I	1 (1.7%)
Stage II	3 (5.1%)
Stage III	11 (18.6%)
Stage IV	35 (59.3)

AML: Acute myeloid leukemia.

DISCUSSION

There is limited data on the safety of endoscopy in patients undergoing treatment with AA for oncological malignancies. Most recently, in a retrospective multi-center study by Kachaamy *et al*[7], the safety of endoscopy was investigated to identify adverse events and mortality in cancer patients being treated with AAs and undergoing endoscopy within 31 d of administration of AAs. It was concluded that endoscopy is well tolerated in patients on AAs and the incidence of adverse events was 0.7%, while the 30 d mortality was estimated at 6.5[7]. In our study, no procedural adverse events were observed, and the mortality rate was 2.35%. One of the two patient succumbed to persistent variceal bleeding, and the other patient died after transition to comfort care.

The first AA to be approved for use was bevacizumab for treatment of breast cancer and since then, AAs have played an integral role in the treatment of many oncological conditions[9]. Various AAs have shown a survival benefit for patients undergoing treatment of colorectal, liver, renal-cell, ovarian,

Table 2 Indication for endoscopic procedures

Indication for endoscopy (*n* = 86)	
GI bleed	29 (33.7%)
Symptomatic (weight loss, abdominal pain, diarrhea, nausea, vomiting, obstruction)	22 (25.6%)
Anemia	5 (5.8%)
Elective diagnostic + follow-up	16 (18.6%)
Dysphagia	9 (10.5%)
Enteral access	5 (5.8%)

GI: Gastrointestinal.

Table 3 Total endoscopic procedures performed and complications

Endoscopic procedures (*n* = 85)	
1 Esophagogastroduodenoscopy	56
(A) With biopsy	17
(B) With variceal banding	10
(C) With stent	2
(D) With pneumatic dilation	1
(E) With percutaneous gastrostomy tube placement	8
(F) Enteroscopy	1
2 Flexible sigmoidoscopy	6
(A) With biopsy	2
3 Colonoscopy	23
(A) With biopsy	7
(B) With snare	3
(C) With control of bleeding	2
(D) With stent placement	1
Complications	
1 Perforation	0
2 Bleeding	2 (2.35%)
Mortality	2 (2.35%)

endometrial, cervical, breast, and gliomas[10-14]. Bevacizumab and other AAs have been associated with poor wound-healing and increases the risk of complications if undergoing surgical and endoscopic procedures. Current literature suggest that the use of bevacizumab and other VEGF inhibitors can impair wound healing and potentially lead to severe wound healing complications[3]. It is therefore recommended to delay elective surgeries for at least 28 d from the time of AA administration[15,16]. At present, there is no recommendation regarding the timing of endoscopic procedures among patients on AAs. Our study indicates that there were no procedure related AEs when AAs were administered within 28 d of an endoscopic procedure including high-risk ones.

Use of AAs have also been associated with an increased bleeding risk. This was demonstrated in a meta-analysis of 38 randomized controlled trials evaluating safety and efficacy of bevacizumab, which revealed a dose-dependent increased risk of bleeding (RR: 1.36 *vs* 2.87)[17]. Another meta-analysis evaluating 22 studies identified an incidence of high-risk bleeding of 2.8% (95%CI 2.1%-3.8%) among patients receiving bevacizumab[18]. In comparison to the findings of the previously mentioned meta-analysis, our study did not identify any patients with post-procedure bleeding. However, one patient had persistent variceal hemorrhage despite attempts for endoscopic control with variceal ligation.

Table 4 List of antiangiogenic agents

Anti-angiogenic agents (*n* = 60)	
Vascular-endothelial growth factor inhibitors	
1 Bevacizumab	30
2 Ramucirumab	3
3 Lenvatinib	4
4 Sorafenib	2
Epidermal-growth factor receptor inhibitors	
1 Cetuximab	3
2 Osimertinib	1
Tyrosine-kinase inhibitors	
1 Lapatinib	1
2 Pazopanib	2
3 Imatinib	7
4 Dasatinib	1
5 Sunitinib	2
Mammalian target of rapamycin inhibitor	
1 Everolimus	2
2 Temsirolimus	2

AAs have also been linked with increased gastrointestinal perforation especially if endoscopic interventions like colonic self-expanding stents (SEMS) are attempted. The rate of perforation ranges between 2%-12% among patients undergoing SEMS placement[19,20]. A meta-analyses evaluating effectiveness and safety of monoclonal antibodies including bevacizumab, cetuximab and panitumumab concluded that the use of these agents have serious adverse events including gastrointestinal perforation[20]. This risk of gastrointestinal perforation, even with the performance of high-risk endoscopic procedures, was not seen in our study which supports the findings of the multicenter outcome study by Kachaamy *et al*[7] regarding the safety of endoscopy among patients on AAs.

Strengths of our study include the removal of any potential selection bias with the inclusion of all patients who underwent endoscopic procedures while on AAs. Given that our facility is not an NCI-designated cancer center, the findings of our study are generalizable and applicable to the general practice. Nonetheless, this study is limited by its retrospective nature and small sample size.

CONCLUSION

In this single center retrospective study, the rate of endoscopic procedure-related adverse events and death within 28 d of AA administration are low. Our study results further support the findings of Kachaamy *et al*[7] on the safety of endoscopy among patients on AAs. While it is recommended to hold AAs 28 d prior to the performance of an elective endoscopic procedure, this should not delay the performance of an emergent or urgent endoscopic procedure given its good safety profile. Our study reiterates the safety data of low-risk endoscopic procedures in this sub-group of patients. This also raises further questions about whether there is a need to hold anti-angiogenics in patients on anti-angiogenics prior to high-risk endoscopic procedures. Awareness of newer medication and its implication on our current practice of gastroenterology are crucial for delivering optimal patient care. Future prospective studies should be evaluated in a multicentric larger population groups while keeping in mind that the GI cancers have an inherent increased risk of bleeding and perforation.

ARTICLE HIGHLIGHTS

Research background

High-grade bleeding and perforation are some of the side effects of antiangiogenic agents. The safety of

endoscopy in patients receiving this therapy is unknown. Here we attempt to explore the incidence of bleeding, perforation, and mortality in our single centered study.

Research motivation

With the increased survival rate of cancer patients with newer chemotherapy, more patients would require endoscopic procedures for further surveillance and screening. It is important to assess the safety of endoscopic procedures among patients receiving therapy such as antiangiogenic agents who are at higher risk for bleeding and perforation.

Research objectives

To understand the risk of endoscopy in patients on antiangiogenic agents.

Research methods

We performed a retrospective analysis of patients, on antiangiogenic agents, who were admitted to the hospital at our institute. We used simple descriptive statistics to primarily assess mortality within 30 d of the procedure along with the incidence of bleeding and perforation.

Research results

We found no procedure-related adverse events in our small population study among the patients receiving antiangiogenic agents. These results need to be further confirmed in a multicentric larger population group.

Research conclusions

Our study reveals that endoscopic procedures are safe in patients receiving antiangiogenic agents. It affirms to not delay emergent or urgent endoscopic procedures among this population.

Research perspectives

Future research should be carried out in a multicentric and larger group of the population than the one in this study to further assess the safety of the endoscopic procedure among this population group.

FOOTNOTES

Author contributions: Azam MU and Hudgi AR performed the research, collected the data, wrote the paper, contributed to analysis and reviewed the article; Uy P collected the data and reviewed the article; Makhija J performed the formal analysis; Yap JE conceptualized, supervised the report and approved the final draft submitted.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Augusta University Medical Centre.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All authors declare that they have no conflict of interest.

Data sharing statement: The technical appendix, statistical code, and dataset are available from the corresponding author at jyap@augusta.edu. Consent was not obtained as this was a retrospective study. No additional data are available.

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ORIGINAL ARTICLE

Randomized Clinical Trial

Feasibility of endoscopic papillary large balloon dilation to remove difficult stones in patients with nondilated distal bile ducts

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Abstract

BACKGROUND

Current guidelines recommend not performing papillary large balloon dilation in patients with nondilated distal bile ducts.

AIM

To assess the feasibility of balloon dilation to remove difficult stones in patients with nondilated distal bile ducts.

METHODS

Data from 1289 endoscopic retrograde cholangiopancreatography (ERCP) procedures were obtained from two prospective studies. While 258 cases had difficult stones (> 1 cm, multiple > 8, impacted, or having a thin distal duct), 191 underwent biliary dilation up to 15 mm after endoscopic sphincterotomy. Cholangiographies of these cases were retrospectively reviewed in order to classify the distal bile duct and both the stone size and number. Primary outcomes were clearance rate at first ERCP and complications.

RESULTS

Of the 191 patients (122 women and 69 men; mean age: 60 years) who underwent biliary dilation for difficult stones, 113 (59%) had a nondilated or tapered distal

duct. Patients with a dilated distal duct were older than those with nondilated distal ducts (mean 68 and 52 years of age, respectively; $P < 0.05$), had more stones (median 4 and 2 stones per patient, respectively; $P < 0.05$), and had less need for additional mechanical lithotripsy (6.4% *vs* 25%, respectively; $P < 0.05$). Clearance rate at first ERCP was comparable between patients with a dilated (73/78; 94%) and nondilated distal ducts (103/113; 91%). Procedures were faster in patients with a dilated distal duct (mean 17 *vs* 24 min, respectively; $P < 0.005$). Complications were similar in both groups (6.4% *vs* 7.1%, respectively).

CONCLUSION

Large balloon dilation for difficult stones is feasible in patients with a nondilated or even tapered distal duct.

Key Words: Difficult bile duct stones; Endoscopic retrograde cholangiopancreatography; Balloon dilation; Complications; Biliary dilation; Cholangiography

Core Tip: Endoscopic papillary large balloon dilation is increasingly being used in treating difficult bile duct stones, since it is faster and less laborious than mechanical lithotripsy, with comparable results in terms of safety and effectiveness. However, this method is not recommended in patients with nondilated distal ducts, due to a higher complication rate, especially perforation. This study evaluated a large cohort of difficult duct stones patients submitted to large balloon dilation and found that patients with dilated and nondilated distal ducts had similar complication rates. This study suggests that large balloon dilation may be feasible in the latter group of patients.

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INTRODUCTION

Endoscopic sphincterotomy with stone extraction by balloon and/or basket is the method of choice for treating bile duct stones[1]. However, in patients with difficult bile duct stones (impacted, multiple or > 1 cm, or having a tapered distal duct), additional methods such as mechanical lithotripsy, intracorporeal lithotripsy, or papillary large balloon dilation are needed. Lithotripsy techniques, especially intracorporeal lithotripsy, which need to be guided by cholangioscopy, increase procedure time, cost, and the number of endoscopic retrograde cholangiopancreatography (ERCP) sessions required to clear the biliary tree[2]. Ersoz *et al*[3] pioneered the use of large balloon dilation of the distal bile duct in order to widen the pre-papillary portion of the common duct and facilitate stone retrieval.

The American Society for Gastrointestinal Endoscopy (ASGE) does not recommend papillary large balloon dilation for nondilated distal ducts because of the "increased risk of perforation"[4]. However, two Japanese studies[5,6] and another by the original technique description by Ersoz *et al*[3] successfully and safely employed endoscopic papillary or biliary large balloon dilation in patients with a nondilated or tapered distal bile duct. The current study analyzes the feasibility of using large balloon dilation of the distal biliary tree to remove difficult stones from patients with a nondilated distal bile duct.

MATERIALS AND METHODS

Data collection

Data were retrieved and analyzed from 1289 ERCPs conducted in two prospective trials during 2014-2019 that assessed post-ERCP pancreatitis (PEP) prevention[7,8]. Eligible subjects were all adults scheduled to undergo ERCP at our institution, and whose cannulation target was the biliary tree. Patients were excluded if they had non-naïve papilla, a previous ERCP at other institutions, failed bile duct cannulation, patients who primarily underwent an infundibulotomy due to an impacted stone at the papilla or papillary neoplasia, Billroth II gastrectomy, or were lost to follow up or refused to enter the studies. All patients gave signed informed consent to the procedure and inclusion in the study. Both

study protocols were approved by the Research Ethics Commission of our Institution and registered in the Brazilian Protocol Registry under UTN codes U1111-1207-7823 (http://www.ensaiosclinicos-.gov.br/rg/RBR-979wh3) and U1111-1176-4646 (http://www.ensaiosclinicos.gov.br/rg/RBR-6zkm5k/. The study was approved by the Institutional Review Board of our hospital and conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, CE, Brazil, 2013). Both trials followed CONSORT guidelines.

In the two randomized trials assessing post-ERCP pancreatitis prevention, 258 cases had difficult bile duct stones (≥ 8 stones, > 1 cm or impacted)[7,8]. Of these, 67 patients had the duct cleared by endoscopic sphincterotomy with or without mechanical lithotripsy and without the need for an endoscopic biliary large balloon dilation (EBLBD) since their distal ducts were wide enough to allow stone passage without balloon dilation. The remaining 191 patients underwent an EBLBD up to 15 mm after a full-length endoscopic sphincterotomy. The operator filled out a procedure evaluation form immediately after the ERCP. The research team, which was blinded to patient randomization, contacted the patients personally or by phone 48-72 h after ERCP and 15-30 d after the procedure to complete the follow-up forms. Patients who experienced post-ERCP pain or bleeding received laboratory and abdominal imaging, or endoscopic evaluation.

Definitions

A nondilated or tapered distal bile duct was defined when the lower part of the biliary tract was < 8 mm in diameter and > 15 mm in length measured by cholangiography. The number of stones and the maximum diameter of each patient's largest stone were independently verified by three of the authors of the present study. Radiographs of the 191 cases who received an EBLBD are stored in our hospital's computer system and were retrospectively evaluated.

Procedure methods

ERCP was performed by one of the authors who performs more than 700 ERCPs annually or by a fellow under supervision. All procedures were performed under sedation with propofol, midazolam, and fentanyl which was supervised by an anesthesiologist. Hyoscine was administered to abolish duodenal peristalsis. After the cholangiographic diagnosis of a difficult stone, a complete sphincterotomy was performed *via* the papillary ostium or the access obtained after pre-cut papillotomy (Jag Wire straight tip, Ultratome XL short nose 20 mm, Microknife XL, Boston Scientific Marlborough, Massachusetts, United States or Tritome triple lumen sphincterotome 25 mm, Tracer Metro Direct wire guide, Huibregtse Triple lumen needle knife 4 mm, Cook Endoscopy, Winston-Salem, NC, United States). A large dilation esophageal/pyloric balloon (CRE PRO Wireguided – esophageal, pyloric, colonic, biliary Balloon Dilatation Catheter 12-15 mm, Boston Scientific, Marlborough, Massachusetts, United States)was inserted into the bile duct and gradually inflated across the papilla at 12-15 mm (3.5-8 ATM according to the manufacturer's recommendations), in order to try and obliterate its waist regardless of the presence of a distal situated stone, a peri-papillary diverticulum, or a nondilated distal duct. Additional upstream dilations in the duct were performed at the endoscopists' discretion if the bile duct distal to the stone was considered not dilated enough to facilitate stone retrieval. For each dilation, the balloon was left inflated in place for 10-30 s. After the EBLBD, a retrieval balloon and/or a basket were used to remove the stones. If stone removal was incomplete, a plastic stent was left in place. Procedure time was measured in minutes from the insertion of the duodenoscope into the patient's oral cavity to its retrieval.

Outcome measurements

The primary outcome was ERCP complications, notably perforation and pancreatitis (PEP). Secondary outcomes were clearance rate at first ERCP, procedure time, and need for mechanical lithotripsy. Procedure-related complications and severity were determined using definitions from a previously published guideline[9].

Statistics

Data were presented as the frequency (percentage) or mean ± SD. The Shapiro-Wilk test was used to assess the normality of the data distribution. The Mann–Whitney test was used to compare continuous variables and a chi-square was used to compare associations between variables. Statistical significance was accepted at a two-sided significance level of 0.05. Statistical analyses were performed using STATA v.15 (STATA Corporation, College Station, Texas, United States).

RESULTS

Of the 191 cases with difficult bile duct stones who received an EBLBD, 122 were women (63.8%) and 69 were men, the mean age was 60 years (range, 26-93 years), and 185 were Caucasians (European-derived) and 6 were black. While 113 of the 191 cases had a nondilated or tapered distal bile duct, 78 had a large distal duct. Cases with a nondilated distal duct had fewer duct stones (mean and median = 2, range, 1-5)

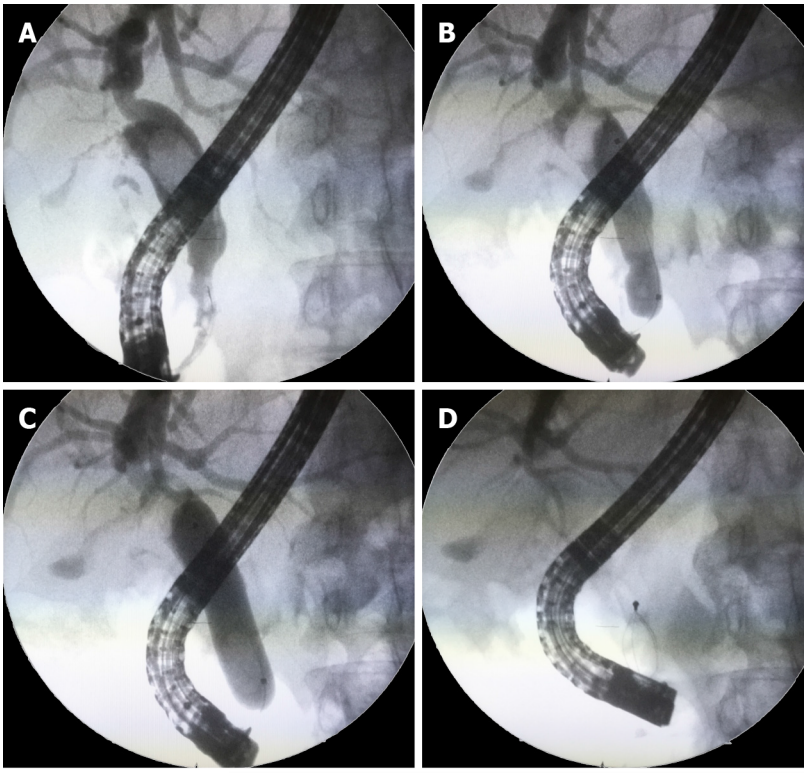

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Figure 1 Large balloon dilation in a patient with tapered distal duct. A: A 60-year-old female patient with a nondilated distal common duct; B: Large balloon dilation of the distal duct; C: Full dilation to 15 mm was performed; D: Stone retrieval without intracorporeal or mechanical lithotripsy was allowed by this technique.

than patients with dilated distal ducts (mean = 4.1, median = 4, range, 1-15; $P < 0.01$). The main bile duct stone size was smaller in patients with nondilated than dilated distal ducts (mean 1.1 cm (range, 0.7-1.5 cm) *vs* 1.7 cm (range, 1.3-2.5 cm), respectively; $P < 0.01$). Patients with a nondilated distal duct were also significantly younger and more likely to have received mechanical lithotripsy (Table 1).

The ERCP technique is described in Figures 1-3. Figure 1 shows a patient with a long intrapancreatic choledochal segment, which was balloon dilated to widen the distal biliary tree and allow easier stone removal after lithotripsy. Figures 2 and 3 show the results from patients with long-segment nondilated distal ducts and impacted stones in the middle common duct. These individuals had large balloon dilation until waist disappearance, resulting in a faster and easier stone extraction in the same sitting.

The clearance rate at first ERCP was comparable between the two groups. Patients with a dilated distal duct had a 94% stone clearance rate (73/78 patients) and those with a nondilated distal duct had a 91% clearance rate (103/113 patients). Procedures were also faster in patients with a dilated than nondilated distal duct (mean = 17 *vs* 24 min, respectively; $P < 0.05$).

The complication rate was similar in both groups. Eight of 113 (7.1%) patients with a nondilated distal duct had complications (two had perforations, three had overt bleedings, and three had PEP), while five of the 78 (6.4%) patients with a large distal duct who received an EBLBD had complications (two had bleeding, one experienced cholangitis, and two had PEP) (Table 2). All complications were treated conservatively and no patients died from the procedure. Of five cases with a dilated distal duct and no bile duct clearance at first ERCP (with a plastic stent left in place), two underwent surgery, and three had their ducts cleared during a second ERCP using lithotripsy techniques. One of these three cases developed fever (mild cholangitis) after the second procedure. In all ten cases with a narrow distal duct for whom the first ERCP attempt failed to complete stone extraction, a second ERCP successfully achieved bile duct clearance. Ductal clearance was accomplished using another EBLBD after stent removal and lithotripsy techniques. Two patients experienced overt bleeding without the need for transfusion and two had mild cholangitis at the second ERCP.

DISCUSSION

In this study, EBLBD up to 15 mm was shown to be feasible and safe for patients with nondilated distal ducts though there were two cases of perforation in this group. Patients with nondilated ducts had the same complication rate of those with dilated distal ducts. An *ex vivo* porcine model showed that biliary

Table 1 The primary features and endoscopic biliary large balloon dilation outcomes of dilated and nondilated distal bile duct patients

	Non-dilated DD (*n* = 113)	Dilated DD (*n* = 78)	*P* value
Mean age (SD)	52 ± 8	68 ± 11	< 0.001
Female/Male	75/38	47/31	0.387
Number of MBD stones (SD)	2 ± 0.7	4.1 ± 2.9	< 0.001
Biggest MBD stone size (SD)	1.1 ± 0.1	1.7 ± 0.2	< 0.001
Additional ML	28 (25%)	5 (6.4%)	0.001

ML: Mechanical lithotripsy; DD: Distal bile duct; MBD: Main bile duct.

Table 2 The complications of dilated and nondilated distal bile duct patients who received endoscopic biliary large balloon dilation

	Non-dilated DD (*n* = 113)	Dilated DD (*n* = 78)
Complication rate, *n* (%)	8 (7.1)	5 (6.4)
Post-ERCP pancreatitis	3	2
Overt bleeding	3	2
Perforations	2	-
Cholangitis	-	1
Death	-	-

ERCP: Endoscopic retrograde cholangiopancreatography; DD: Distal bile duct.

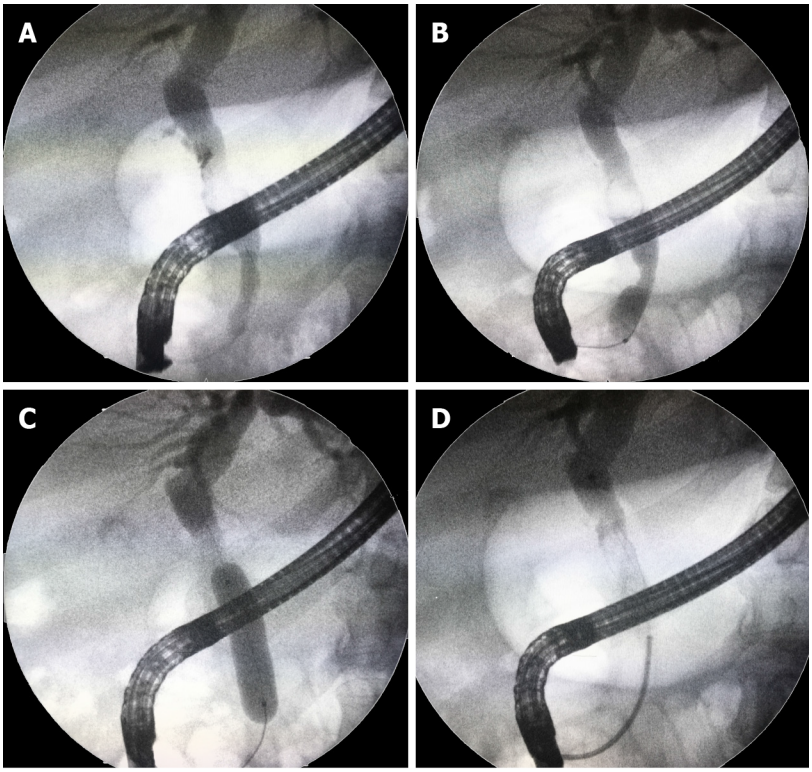

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Figure 2 Large balloon dilation in a patient with a long nondilated distal duct segment. A: A patient with a long non-dilated distal duct and impacted stone; B: Beginning of balloon dilation with choledochal waist; C: Full dilation to 15mm was obtained; D: Stone removal without the need of lithotripsy.

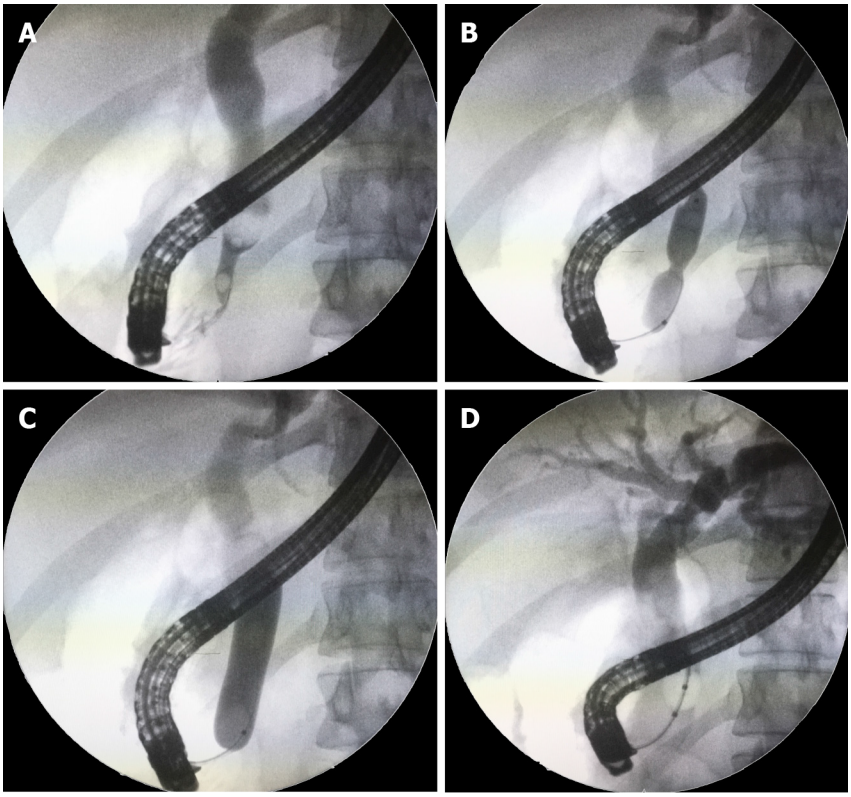

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Figure 3 Large balloon dilation technique. A: Cholangiography demonstrates an impacted stone above a nondilated distal duct in a young patient; B: Balloon dilation at the tapered distal common duct segment with a balloon waist still observed; C: Full dilation up to 15 mm pushing the stone upstream; D: Balloon stone extraction is achieved.

duct tears are caused by overdistention of narrow ducts after large balloon dilation[10]. However, studies indicate that a tear in a nondilated distal bile duct in humans does not necessarily result in a retroperitoneum or peritoneal cavity rupture because this thinner portion is located within the pancreas [10]. This is one explanation for why only two of 113 (< 2%) patients with nondilated distal bile ducts who received EBLBD experienced overt perforations. Despite physical compression resulting from balloon dilation inside the pancreatic head, PEP rates were relatively low and similar in both groups (2.7% *vs* 2.6% for patients with non-dilated and dilated distal bile ducts, respectively). Another possible explanation for our findings was the fact that we always dilate the bile duct and the ampullary region with balloons up to 15 mm. In a Korean study analyzing 672 EBLBD for difficult stones, perforations and fatal complications only occurred in patients dilated > 15-20 mm. No perforation was observed in patients dilated 12-15 mm[11].

ASGE guideline C level recommendation that EBLBD should not be performed in patients with a nondilated distal duct is based on one study in which three deaths occurred as a result of perforation following EBLBD and, in two of the three cases, a full incision sphincterotomy was also performed[4,12]. The guideline used the same study to recommend at evidence level of III that the maximum diameter of the balloon should not exceed that of the distal common bile duct[4,12]. Fujita *et al*[5] analyzed 209 cases submitted to EBLBD and found no differences in the incidence of PEP, bleeding, or perforation when comparing EBLBD in patients with and without a nondilated distal bile duct. Ersoz *et al*[3], the first endoscopists who employed large balloon dilation for difficult stones, evaluated 18 cases with a nondilated distal duct and 40 with a dilated distal duct in their original report. There were no cases of perforations in either group, but bleeding occurred more often in patients with a nondilated distal duct.

In patients with large stones and no distal duct dilation, a common finding in our experience, it can be more difficult and labor-intensive to clear the common duct. As a result of stone impaction in the pre-papillary portion of the bile duct, this process usually requires multiple mechanical lithotripsies and stone retrieval with baskets until extraction balloons can be used. EBLBD has been avoided and contraindicated in these cases[4]. Based on the original report by Ersoz *et al*[3] and two additional series [5,6], we hypothesized that EBLBD could be extended to patients with a nondilated distal bile duct. In our technique, we perform additional dilations in the proximal part of the duct and found that the full balloon length could frequently be inserted into the bile duct. As a result, we named this technique "endoscopic biliary large balloon dilation" and not papillary dilation as usually described. The goal of EBLBD is to create a wide opening in the distal biliary tree and papillary orifice to facilitate stone

removal using extraction balloons or baskets. Importantly, this patient population is more difficult to manage even with the help of EBLBD in those with a nondilated distal duct. In the current study, patients with a nondilated distal duct were more likely to require mechanical lithotripsy (25% *vs* 6.4% for those with a nondilated and dilated distal duct, respectively) despite having significantly smaller stones and a lower number of stones than those with a dilated distal duct. This may be because even dilating the distal duct to 8 ATM (according to the manufacturer's instructions, this pressure should theoretically dilate the duct to 15 mm), the promised duct width of more than 1 cm is not actually reached, as we observed in our practice. An explanation for this phenomenon is that the distal portion of the bile duct is located within the pancreas.

The use of sphincterotomy plus EBLBD significantly reduces the use of mechanical lithotripsy and procedural time in comparison to sphincterotomy alone, as demonstrated by a French multicenter study only evaluating patients with wide distal ducts, since these authors excluded patients with "stenotic" distal ducts[13]. In 150 difficult stone cases, the use of sphincterotomy plus EBLBD had the same complication rate as sphincterotomy alone and presented a higher clearance rate at the initial ERCP[13]. A meta-analysis of six other studies reached similar conclusions[14]. Of note, patients with nondilated distal ducts are more difficult to manage and were not included in these studies[13,14]. The use of EBLBD in patients with nondilated distal bile ducts would reduce the use of lithotripsy, shorten procedure time, and—in a cost containment reality such as ours—would significantly reduce costs by avoiding the employment of cholangioscopy-guided lithotripsy. In a general population of difficult stone patients, EBLBD is demonstrated to be as safe and as effective as single operator cholangioscopy-guided lithotripsy[15].

There are limitations to the current study. Data were extracted from two prospective randomized controlled trials evaluating PEP prevention and not difficult stone management. Data were retrospectively collected by reviewing the cholangiographies of the 191 patients who underwent EBLBD. The indications for EBLBD may not have been standardized in the sample, despite its single-center nature, since treatment for difficult choledocholithiasis was not the aim of the study. On the other hand, this study analyzed a significant sample of large biliary balloon dilated patients with nondilated distal ducts and we ensured that they were prospectively evaluated for complications given their involvement in two prospective trials.

CONCLUSION

EBLBD for stone removal may be feasible and effective option for patients with a nondilated or tapered distal bile duct and may be a significantly less costly and time-saving alternative to cholangioscopy-guided intracorporeal lithotripsy. Our technique, in which proximal parts of the duct and not just the pre-papillary region are dilated, may explain the success of EBLBD. This method requires prospective validation by future studies.

ARTICLE HIGHLIGHTS

Research background

Endoscopic papillary large balloon dilation is increasingly being used in treating difficult bile duct stones, since it is faster and less laborious than performing multiple mechanical lithotripsies, with comparable results in terms of safety and effectiveness. However, this method is not recommended in patients with nondilated distal bile ducts, due to a theoretically higher complication rate, especially perforation.

Research motivation

Papillary large balloon dilation is an important tool to extract difficult duct stones and very few studies examined this technique in patients with nondilated distal ducts, although in its original report, this method was used in this setting.

Research objectives

To analyze the feasibility of papillary large balloon dilation in patients with difficult bile duct stones and nondilated distal bile ducts, as well as the complication rate and effectiveness of this method in this subset of stone patients. To investigate the demographic characteristics of this patient group. Data on these issues may stimulate future research and assist endoscopists in choosing the best endoscopic modality to treat difficult bile duct stones.

Research methods

We retrieved data from 1289endoscopic retrograde cholangiopancreatography (ERCP) procedures from

2 prospective randomized controlled trials dealing with post-ERCP pancreatitis (PEP). Of these, 258 cases had difficult stones (> 1 cm, multiple > 8, impacted, or having a thin distal duct) and 191 underwent papillary large balloon dilation up to 15 mm after endoscopic sphincterotomy for stone retrieval. Cholangiographies of these cases were retrospectively reviewed by the authors in order to classify the distal bile duct as dilated or nondilated, as well as stone size and number. Primary outcomes were clearance rate at first ERCP and complications.

Research results

Of the 191 patients, 113 (59%) had a nondilated or tapered distal duct (75 F/38 M, mean age: 52 years) and 78 (47 F/31 M mean age: 68 years) a dilated distal duct. Cases with a nondilated distal duct had fewer (mean = 2 *vs* 4.1, $P < 0.05$) and smaller (mean 1.1 cm *vs* 1.7 cm, $P < 0.05$) stones than those with a dilated distal duct and were significantly younger than patients with dilated distal). Patients with a nondilated distal duct were also significantly younger and more likely to receive mechanical lithotripsy (25% *vs* 6.4%, $P < 0.05$). Clearance rate at first ERCP was comparable between patients with a dilated (73/78; 94%) and nondilated distal ducts (103/113; 91%). Procedures were faster in patients with a dilated distal duct (mean 17 *vs* 24 min, $P < 0.005$). Complications were similar in both groups: 8/113 (7.1%) *vs* 5/78 (6.4%), however the 2 perforations occurred in patients with nondilated ducts. There was no mortality.

Research conclusions

Large balloon dilation for difficult stones is feasible in patients with a nondilated or even tapered distal duct. Although the latter patients had smaller stones, they are more difficult to remove, since ERCP procedures in these patients require mechanical lithotripsy more often and last longer.

Research perspectives

Future prospective multicenter studies should evaluate the feasibility of large balloon dilation in patients with nondilated distal bile ducts and difficult stones, since current guidelines do not recommend the procedure in this group of patients.

FOOTNOTES

Author contributions: Pereira Lima JC, Saifert Moresco G, Sanmartin IDA, Contin I, Pereira-Lima G, Watte G, Altmayer S, Oliveira dos Santos CE, have been involved equally and have read and approved the final manuscript; Pereira Lima JC, Saifert Moresco G, Sanmartin IDA, Contin I, Pereira-Lima G, Watte G, Altmayer S, Oliveira dos Santos CE meet the criteria for authorship established by the International Committee of Medical Journal Editors and verify the validity of the results reported.

Institutional review board statement: This study and protocols were approved by the Research Ethics Commission of our Institution and registered in the Brazilian Protocol Registry under number RBR-979wh3 (http://www.ensaiosclinicos.gov.br/rg/RBR-979wh3) and UTN Number: U111-1207-7823 (URL: http://www.ensaiosclinicos.gov.br/rg/RBR-6zkm5k/). Written informed consent was obtained from all patients. The study adheres to the declaration of Helsinki.

Clinical trial registration statement: Brazilian Protocol Registry under number RBR-979wh3 (http://www.ensaiosclinicos.gov.br/rg/RBR-979wh3) and UTN Number: U111-1207-7823 (URL: http://www.ensaiosclinicos.gov.br/rg/RBR-6zkm5k/).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Prof. Dr. Julio Pereira Lima (jpereiralima@terra.com.br) is on the speakers' board of Takeda Pharmaceutical Latin America and receives honoraria as consultant of Boston Scientific, Latin America and Cook Endoscopy, Brazil. Dr. Carlos Eduardo Oliveira dos Santos (ddendo@uol.com.br) receives speaker fees and is a consultant of the speakers' board of Fujinon Co., Latin America. Drs. Giusepe Saifert Moresco (giusepemoresco@outlook.com), Ivan David Arciniegas Sanmartín (davidarciniegas23@gmail.com), Isabela Contin (isabeladbcontin@gmail.com), Guilherme Pereira Lima (guilhermepl14@gmail.com), Guilherme Watte (g.watte@gmail.com), and Stephan Altmayerstephanaltmayer@gmail.com) have no conflicts of interest or financial ties to disclose.

Data sharing statement: Dataset available from the corresponding author at pereiralimajulio@gmail.com. Participants gave informed consent for data sharing.

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SYSTEMATIC REVIEWS

Role of balloon enteroscopy for obscure gastrointestinal bleeding in those with surgically altered anatomy: A systematic review

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Abstract

BACKGROUND

Obscure gastrointestinal (GI) bleeding is defined as persistent bleeding despite negative evaluation with both esophagogastroduodenoscopy and colonoscopy and can be secondary to small intestinal pathology. Standard endoscopy as well as push endoscopy can be a challenge in those with altered anatomy given inaccessible areas as well as perforation risk. Single and double balloon enteroscopy can be warranted in this patient population in instances of obscure GI bleed.

AIM

To assess the safety and diagnostic efficacy of balloon enteroscopy for obscure GI bleeding in patients with surgically altered anatomy.

METHODS

A search was conducted through PubMed, MEDLINE, Google Scholar, Scopus, and Embase with the key words "enteroscopy," "obscure bleeding," and "altered anatomy," to identify relevant articles in English with no restricted time frame. A search within the Reference Citation Analysis database was conducted to ensure inclusion of the latest high impact articles. Study types included in the review were prospective and retrospective reviews, case series, and case reports. The reference lists of these papers were also reviewed to find further papers that were applicable. The authors extracted the data from the studies that fit inclusion criteria. Data of interest included type of study, type of procedure, and type of altered anatomy, as well as the number of patients with any diagnostic or therapeutic intervention. Data was also recorded on procedure tolerance and complications. The data was analyzed with descriptive statistics.

RESULTS

Our literature search yielded 14 studies that were included. There were 68 procedures performed with 61 unique patients subjected to these procedures. Forty-four (65%) of the procedures were double balloon, 21 (31%) were single balloon, and 3 (4%) were classified as through the scope balloon assisted. The most common altered anatomy types included Gastric Bypass Roux-en-Y, Pylorus Sparing Whipple, Orthotopic Liver Transplantation with Roux-en-Y, and Gastrojejunostomy Roux-en-Y. The procedures were successfully performed in each patient. There were 5 (7%) procedures that were complicated by perforation. Amongst the available data, the diagnostic yield was 48/59 (81%) and a therapeutic yield of 39/59 (66%). One patient was recommended surgical revision of their altered anatomy following enteroscopy.

CONCLUSION

Balloon enteroscopy is a useful diagnostic modality in investigating obscure GI bleeding within those with surgically altered anatomy; however, precautions must be taken as this population may have increased perforation risk.

Key Words: Altered anatomy; Single balloon enteroscopy; Double balloon enteroscopy; Obscure; Bleed; Gastrointestinal

Core Tip: Balloon enteroscopy is often warranted in patients with surgically altered anatomy who suffer from obscure gastrointestinal (GI) bleeding. Data remain limited on the clinical utility of single or double balloon enteroscopy in those with altered anatomy. The primary aim of this systematic review was to assess the diagnostic and therapeutic efficacy of balloon enteroscopy for obscure GI bleeding in patients with surgically altered anatomy. The secondary aim was to investigate the safety of balloon enteroscopy in this patient population.

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INTRODUCTION

Obscure gastrointestinal (GI) bleeding is defined as persistent bleeding despite negative evaluation with both esophagogastroduodenoscopy and colonoscopy. Most obscure GI bleeding can be secondary to small intestinal pathology and has now become manageable with the introduction of single balloon enteroscopy (SBE) or double balloon enteroscopy (DBE) in 2001[1]. The overall diagnostic utility of DBE has ranged from 59%-90%[2-5]. In patients with surgically altered anatomy, endoscopic procedures may be challenging. Given distortion of native anatomy, areas that may have been accessible with standard endoscopy may be inaccessible or difficult to reach. In such instances, anastomotic areas remain at risk for perforation especially when larger diameter endoscopes are inserted at longer lengths. Deep enteroscopy can also be implemented to access sites unreachable by standard endoscopy[6]. Those with distorted anatomy may require thorough investigation of the upper GI tract in instances such as refractory abdominal pain or obscure GI bleeding. Balloon enteroscopy can be warranted in such cases where standard and push endoscopy are unrevealing.

SBE and DBE have been shown to be effective in patients with surgically altered anatomy in regards to endoscopic retrograde pancreatography (ERCP) and biliary complications. However, there remains limited information regarding management of obscure GI bleeding in patients with surgically altered anatomy. This systematic review aims to assess the overall safety and diagnostic efficacy of balloon enteroscopy for obscure GI bleeding in patients with surgically altered anatomy.

MATERIALS AND METHODS

Literature search

Data for this review was identified and performed by two independent reviewers (MA, TC) with

consensus to avoid bias. Discrepancies and the decision over whether to include or exclude a study were resolved by means of discussion with consensus to avoid bias. Searches were done on PubMed, Google Scholar, Scopus, and Embase. All relevant articles were carefully reviewed with a review of each article's references as well. Terms used for the search included "enteroscopy," "obscure bleeding," "gastrointestinal bleeding," and "altered anatomy." The literature search was performed in December 2021. Study types included in the review were prospective and retrospective reviews, case series, and case reports. Reference lists from these articles were also reviewed to find pertinent articles. Inclusion criteria for our systematic review included studies that were subjected to peer review and had available text in English. Only studies accessible through the search engines listed above were included in our review. Solitary abstract reports were excluded from our study in addition to any studies performed on animals. Studies that were not subject to peer review or were of pediatric focus (< 18 years) were also excluded from the study. A specific PRISMA flow diagram is included in Figure 1 to summarize our search methods. A further literature search was conducted with the reference citation analysis (RCA) engine, an artificial intelligence technology-based open multidisciplinary citation analysis database (https://www.referencecitationanalysis.com). This database was implemented to ensure the latest high impact articles were included in our study. Following a search of "balloon enteroscopy" within the RCA database no further studies were identified that fit our inclusion criteria.

Data from each study were extracted into an excel file in a systematic fashion. Extracted data included type of study, type of procedure, and type of altered anatomy, as well as the number of patients with any diagnostic findings or therapeutic intervention. Data were also recorded on procedure tolerance and complications. Due to the lack of controlled trials, retrospective and prospective observational studies were also included, as were case reports. We considered all clinical studies or reports that had been published until December 2019. As the current work only involved previously performed studies, approval by the Institutional Review Board or individual patient consent was deemed unnecessary.

Statistical analysis

Statistical analysis in the form of descriptive statistics was reported from each study. This data was organized and included in a structured table (Table 1).

RESULTS

Following the search of these databases, 14 studies in total were included in our review. Of these studies, 6 were retrospective studies[7-12], 2 were prospective studies[13,14], 1 was a case series[15], and the remaining 5 were case reports[16-20]. In total, there were 68 procedures performed with 61 unique patients that had undergone these procedures. All patients were above the age 17 years old at the time of procedure. Forty-four (65%) of the procedures were double balloon, 21 (31%) were single balloon, and 3 (4%) were classified as through the scope balloon assisted. There were a variety of altered anatomy types with the most common being Gastric bypass Roux-en-Y (GBR), Pylorus sparing Whipple (PSW), Orthotopic Liver Transplantation with Roux-en-Y (OLTR), and Gastrojejunostomy Roux-en-Y (GJR).

The procedures (SBE *vs* DBE) were performed in all patients; however, five (7%) procedures were complicated by perforation. There were no reported complications in the remaining 63 (93%) patients. Amongst the 5 reported procedure related perforations, 2 (40%) patients had a Roux-en-Y. The remaining 3 patients consisted of an ileal-sigmoid anastomosis, a right hemicolectomy with ileostomy, and an unspecified altered anatomy type. From the available data in each study, there was an overall diagnostic yield of 48/59 (81%) and a therapeutic yield of 39/59 (66%). Common diagnostic findings included ulcers (Figure 2A), arteriovenous malformations, angioectasia, anastomotic site bleeding (Figure 2B), and other post-surgical bleeding (Figure 2C). Therapeutic interventions consisted of argon plasma coagulation (APC), endoscopic clip placement, epinephrine injection, and N-butyl-2-cyanoacrylate (Histoacryl) injection. There was 1 patient who was recommended surgical revision of their altered anatomy following enteroscopy.

DISCUSSION

Obscure GI bleeding accounts for 5% of all GI bleeds with the culprit most often being small bowel origin[21]. Balloon enteroscopy has been implemented to assess for obscure GI bleeding and can be performed through different approaches. SBE utilizes an enteroscope (200 cm in length) with an overtube (140 cm in length) and balloon inflation device. DBE on the other hand has the same enteroscope and overtube but consists of two balloons: one at the tip of the enteroscope and the other acting as an anchoring leverage on the distal part of the overtube. These procedures can be performed anterograde (through the mouth) or retrograde (through the anus)[21].

Despite the differences in the devices, the techniques for these procedures are similar. The overtube is backloaded on the enteroscope after which the enteroscope is advanced deeply into the small intestine.

Table 1 Overview of literature on balloon enteroscopy for obscure gastrointestinal bleeding in those with altered anatomy

Cases (*n*-patients)	Anatomy	Device	Study type	Yield	Complications	Ref.
17 (12)	8 GBR, 6 PSW, 2 OLTR, 1 GJR	DBE	Retrospective	15/17 diagnostic; 14/17 therapeutic	1/17 perforation	[7]
3 (3)	Not specified	TTS-BAE	Retrospective	1/3 diagnostic; 1/3 therapeutic	None	[8]
3 (3)	1 OLTR, 1 Ileal-sigmoid anastomosis, 1 right hemicolectomy with ileostomy	DBE	Retrospective	3/3 diagnostic; 0/3 therapeutic	3/3 perforation	[9]
15 (15)	Not specified	SBE	Retrospective	8/15 diagnostic; 5/15 therapeutic	None	[10]
3 (1)	Most OLTR	DBE	Retrospective	3/3 diagnostic; 1/3 therapeutic	None	[11]
5 (5)	Not specified	DBE	Retrospective	5/5 diagnostic; 5/5 therapeutic	None	[12]
9 (9)	Not specified	DBE	Prospective	Does not specify	1/9 perforation	[13]
3 (3)	3 GBR	DBE	Prospective	3/3 diagnostic; 3/3 therapeutic	None	[14]
5 (5)	2 HJ, 1 PSW, 1 GBR, 1 right hemihepatectomy w/RYHJ	3 DBE 2 SBE	Case Series	5/5 diagnostic; 5/5 therapeutic	None	[15]
1 (1)	OLTR	SBE	Case Report	1/1 diagnostic; 1/1 therapeutic	None	[16]
1 (1)	HJ	SBE	Case Report	1/1 diagnostic; 1/1 therapeutic	None	[17]
1 (1)	Whipple	DBE	Case Report	1/1 diagnostic; 1/1 therapeutic	None	[18]
1 (1)	GBR	SBE	Case Report	1/1 diagnostic; 1/1 therapeutic	None	[19]
1 (1)	OLT	SBE	Case Report	1/1 diagnostic; 1/1 therapeutic	None	[20]

TTS-BAE: Through the scope balloon assisted enteroscopy; GBR:Gastric bypass Roux-en-Y; PSW: Pylorus sparing Whipple; OLTR: Orthotopic Liver Transplantation with Roux-en-Y; OLT: Orthotopic Liver Transplantation; GJR: Gastrojejunostomy Roux-en-Y; HJ: Hepaticojejunostomy; RYHJ: Roux-en-Y hepaticojejunostomy.

Anchoring of the endoscope is secured by the balloon tip on the enteroscope in DBE *vs* the flexible tip with no balloon assisted anchoring in SBE. The overtube with its deflated balloon is advanced all the way to the distal tip of the enteroscope. Once the overtube has reached the distal end of the enteroscope, a stepwise pattern of inflation and deflation of the single *vs* double balloon apparatus is used to assist enteroscope transit in visualizing the area of small bowel[21,22].

The SBE model frequently utilized is the Olympus SIF-Q180 with an outer diameter of 13.2 mm, inner diameter of 11 mm, and balloon diameter of 40mm. DBE models are developed by Fujinon and consist of the EN-450T5, EN-450PS/20, and the EC-450BI5 with outer diameter ranging from 12.2-13.2 mm, inner diameter ranging from 10-10.8 mm, and balloon diameter being 40 mm[23].

Obscure GI bleeding has been estimated to account for 5%-10% of all GI bleeding, with increasing number of patients requiring balloon enteroscopy for small bowel evaluation[24]. The diagnostic yield of balloon enteroscopy amongst those without altered anatomy has been reported around 45%-55%[21,25]. Adverse rates are overall low at 3.2% with most common complications including intestinal bleeding, perforation, or post-procedure pancreatitis[26,27]. With the emerging surgical techniques for various GI pathologies, surgically altered GI anatomy remains prevalent. The obesity epidemic in the United States has led to increased referrals to bariatric surgeries. Additionally, the advancements in liver transplant (LT) have led to increasing number of patients receiving LT over the past several years [28]. Given their surgically altered GI anatomy, these patients remain at risk for GI bleeding. Furthermore, the management of these patients may be complicated by surgical anastomotic sites often serving as culprits of obscure GI bleeding[7,17,18]. These patients may require work up leading to SBE or DBE for underlying diagnosis.

Besides a substantial diagnostic yield, therapeutic interventions can be effectively achieved using the enteroscope channel. Balloon enteroscopy allows the endoscopist to safely deploy and advance ablation catheters, injection needles, and mechanical or hemostatic clips. These devices can even be modified to

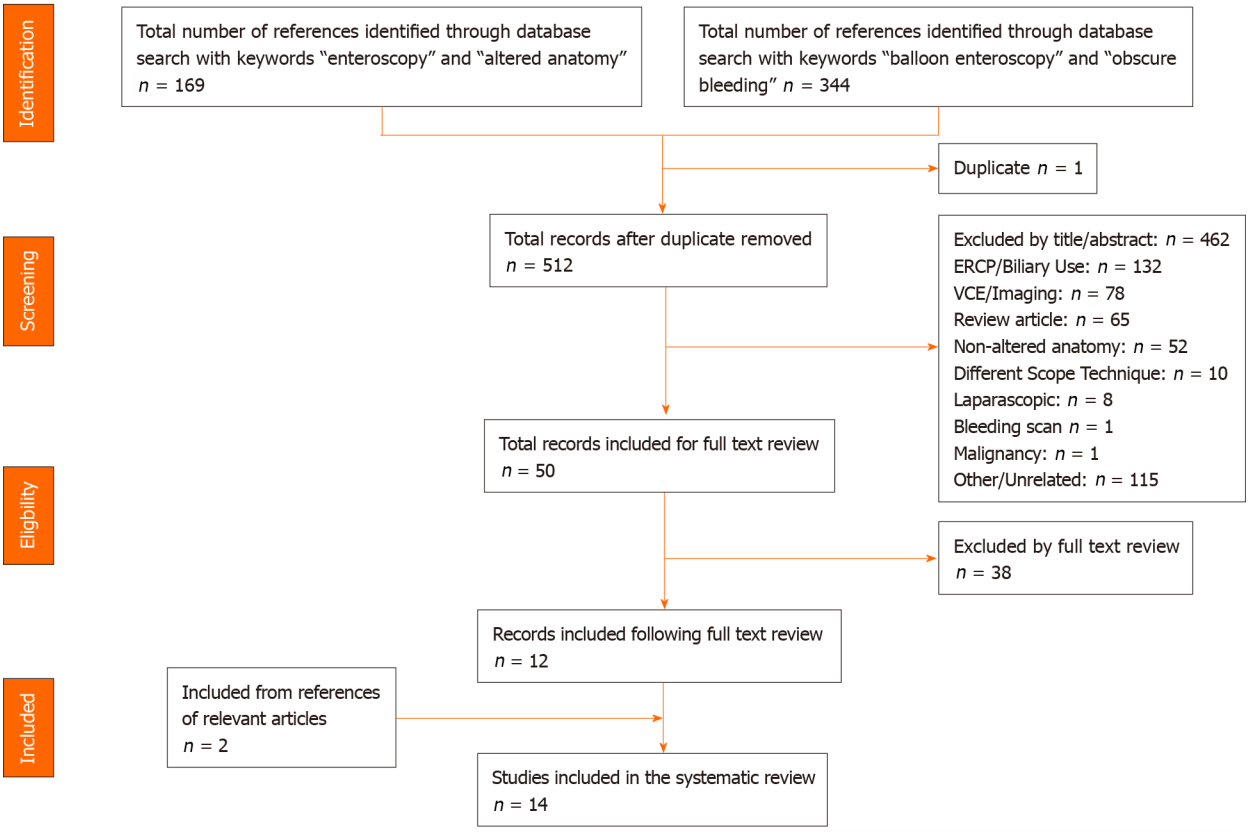

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Figure 1 Prisma diagram of literature review.

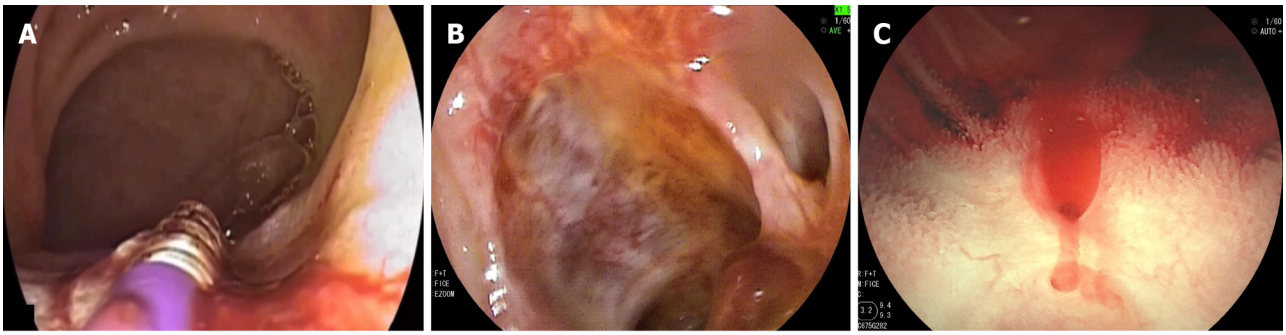

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Figure 2 Balloon enteroscopy. A: Endoscopic depiction of a bleeding duodenal ulcer undergoing thermal therapy in a post RYGB patient; B: Visualization of anastomotic neovascularization and bleeding in a patient with hepaticojejunostomy; C: Illustration of intraluminal bleeding in a patient following pancreatojejunostomy at the surgically altered site.

deliver Hemospray®. According to our literature, perforation remains the most frequently reported complication following balloon enteroscopy in those with altered anatomy. Post-surgical small bowel adhesions are prone to tearing during enteroscopy which can lead to perforation. Overall perforation rates in enteroscopy amongst those with both unaltered and altered anatomy from meta-analysis data have been reported to be as low as 0.24%[10,29,30]. Colonoscopy and upper endoscopy on the other hand have perforation rates as low as 0.1%[31]. From the available literature in this review, perforation rates were as high as 7% in those with surgically altered anatomy requiring single or double balloon enteroscopy. Such risk should be considered by clinicians during procedure planning in this patient population. Notably, the presence of post-surgical adhesions and overtube maneuvering through tight bends can be potential factors leading to added complications. The use of fluoroscopy can aid in navigating the enteroscope in challenging situations.

GBR, PSW, OLTR, and GJR were the most reported altered anatomy types observed in our review. The various types of altered anatomy structures may have an impact on the underlying procedure regarding luminal passage and scope maneuvers. No trend was identified regarding an association

between diagnostic or therapeutic yield with altered anatomy types. We observed that 20% of the perforations were seen in patients with a Roux-en-Y. Those with altered small bowel anatomy may be more prone to suffer procedure related complications; however, further work is needed to verify these findings.

When compared to previous systematic reviews of balloon assisted ERCP in those with surgically altered anatomy, our study has notable differences. Diagnostic yields have varied between 70%-90% with procedure success rates approaching 62%-93% amongst single or double balloon assisted ERCP[32-34]. These studies depicted overall adverse event rates between 4%-7% with perforations making up a minority of these complications[32-34]. Such variance from our study may stem from the purpose of procedure with balloon enteroscopy for obscure GI bleeding requiring a thorough investigation of the small bowel, whereas balloon assisted ERCP typically focuses on assessment and interventions within the biliary tree. Although both procedures can be technically challenging, underlying maneuvers and interventions can vary. The higher incidence of perforation rate in our study when compared to balloon assisted ERCP may be attributed to aspects related to altered anatomy including procedure time, more extended exploration of the small bowel, presence of underlying adhesions and different targeted therapeutic techniques. Further studies are needed to further characterize these differences.

We recognize that our study has limitations. Foremost, given the small number of relevant published literature on this topic, our review is limited by a small sample size within these 14 reports. The lack of extensive literature that fits our inclusion criteria highlights the need for further studies to continue to assess the role of balloon enteroscopy in surgically altered anatomy patients. Additionally, most of our accessed studies being retrospective in nature as well as inclusion of case reports without controlled studies limit the conclusions taken from our review. Given the limited availability of studies to fit our inclusion criteria, we included case reports which may have skewed our overall results given many having 100% diagnosis rates and 0% complication rates. Furthermore, we were unable to perform analysis based on the procedure approach (retrograde *vs* anterograde) given reporting variability amongst the studies. The variety of altered anatomy types and the variability in data reporting in each of these studies also places further limits on the generalizability of our findings.

CONCLUSION

Our systematic review indicates that the data on the clinical utility of balloon enteroscopy in the evaluation of small bowel bleeding remains limited in those with surgically altered anatomy. The compiled data from the available literature demonstrates that balloon enteroscopy represents a clinically useful diagnostic modality in identifying culprit lesions for this subset of patients with diagnostic and therapeutic yields as high as 83% and 64% respectively. However, precautions and appropriate selection of cases must be taken within this patient population with an incidence of perforation as high as 7%.

ARTICLE HIGHLIGHTS

Research background

Obscure gastrointestinal (GI) bleeding is defined as persistent bleeding despite negative evaluation with both esophagogastroduodenoscopy and colonoscopy and is often secondary to small intestinal pathology. This form of GI bleeding has now become manageable with the introduction of single balloon enteroscopy or double balloon enteroscopy. Those with distorted anatomy may require thorough investigation of the upper GI tract during obscure GI bleeding, and balloon enteroscopy may be warranted.

Research motivation

Balloon enteroscopy can be warranted in instances of obscure GI bleeding in those with altered anatomy; however, literature remains limited on the overall diagnostic and therapeutic yields as well as the overall safety of these procedures in this patient population.

Research objectives

The primary aim of this systematic review was to assess the diagnostic and therapeutic efficacy of balloon enteroscopy for obscure GI bleeding in patients with surgically altered anatomy. The secondary aim was to investigate the safety of balloon enteroscopy in this patient population.

Research methods

We performed an extensive literature search on PubMed, Google Scholar, Scopus, and Embase where relevant articles were carefully reviewed. Terms used for the search included "enteroscopy," "obscure bleeding," "gastrointestinal bleeding," and "altered anatomy." Further search with the Reference

Citation Analysis database was conducted to ensure inclusion of the latest high impact articles. Prospective and retrospective reviews, case series, and case reports were all included. Data from each study that fit our inclusion criteria were extracted into an excel file in a systematic fashion. Statistical analysis in the form of descriptive statistics was reported from each study.

Research results

Following our literature search, 14 studies were included in our review. In total, there were 68 procedures performed with 61 unique patients that had undergone these procedures. From the available data in each study, there was an overall diagnostic yield of 48/59 (81%) and a therapeutic yield of 39/59 (66%). Five (7%) procedures were complicated by perforation.

Research conclusions

Our systematic review shows that balloon enteroscopy can be implemented in obscure GI bleeding in those with altered anatomy. Diagnostic and therapeutic yields were as high as 83% and 64% respectively. Given the overall perforation of 7%, caution is warranted in such cases. Further literature is needed to expand upon our findings.

Research perspectives

Balloon enteroscopy remains a viable option to investigate obscure GI bleeding in those with altered anatomy. Caution is warranted given the reported perforation rates; however, further studies are needed to add to the limited available literature.

FOOTNOTES

Author contributions: Aryan M, Colvin T, and Shajan P designed the research; Aryan M and Colvin T performed the systematic review; Aryan M analyzed the data; Aryan M, Colvin T, and Shajan P wrote the paper; Shajan P, Kyanam Kabir Baig KR, and Ahmed A supervised the paper; all authors read and approved the final manuscript.

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SYSTEMATIC REVIEWS

Quality of life after surgical and endoscopic management of severe acute pancreatitis: A systematic review

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Abstract

BACKGROUND

Treatment for severe acute severe pancreatitis (SAP) can significantly affect Health-related quality of life (HR-QoL). The effects of different treatment strategies such as endoscopic and surgical necrosectomy on HR-QoL in patients with SAP remain poorly investigated.

AIM

To critically appraise the available evidence on HR-QoL following surgical or endoscopic necrosectomy in patient with SAP.

METHODS

A literature search was performed on PubMed, Google™ Scholar, the Cochrane Library, MEDLINE and Reference Citation Analysis databases for studies that investigated HR-QoL following surgical or endoscopic necrosectomy in patients with SAP. Data collected included patient characteristics, outcomes of interventions and HR-QoL-related details.

RESULTS

Eleven studies were found to have evaluated HR-QoL following treatment for severe acute pancreatitis including 756 patients. Three studies were randomized

trials, four were prospective cohort studies and four were retrospective cohort studies with prospective follow-up. Four studies compared HR-QoL following surgical and endoscopic necrosectomy. Several metrics of HR-QoL were used including Short Form (SF)-36 and EuroQol. One randomized trial and one cohort study demonstrated significantly improved physical scores at three months in patients who underwent endoscopic necrosectomy compared to surgical necrosectomy. One prospective study that examined HR-QoL following surgical necrosectomy reported some deterioration in the functional status of the patients. On the other hand, a cohort study that assessed the long-term HR-QoL following sequential surgical necrosectomy stated that all patients had SF-36 > 60%. In the only study that examined patients following endoscopic necrosectomy, the HR-QoL was also very good. Three studies investigated the quality adjusted life years suggesting that endoscopic and surgical approaches to management of pancreatic necrosis were comparable in cost effectiveness. Finally, regarding HR-QoL between open necrosectomy and minimally invasive approaches, patients who underwent the later had a significantly better overall quality of life, vitality and mental health.

CONCLUSION

This review would suggest that the endoscopic approach might offer better HR-QoL compared to surgical necrosectomy. However, the available comparative literature was very limited. More randomized trials powered to detect differences in HR-QoL are required.

Key Words: Acute pancreatitis; Pancreatic necrosis; Surgical necrosectomy; Endoscopic necrosectomy; Minimally invasive drainage; Quality of life

Core Tip: Acute pancreatitis is a common disease with potentially life-threatening complications. Treatment for severe acute pancreatitis can significantly affect health-related quality of life (HR-QoL). The effects of different treatment strategies such as endoscopic and surgical necrosectomy on HR-QoL remain poorly investigated. In this review, we critically analyze the available evidence on HR-QoL following treatment for severe acute pancreatitis. It could be suggested that endoscopic necrosectomy could offer better HR-QoL compared to surgical necrosectomy.

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INTRODUCTION

Acute pancreatitis is a common disease with potentially serious complications. Most patients present with a mild and self-limiting disease which is associated with low morbidity and mortality[1]. However, some patients present with moderate to severe or severe acute pancreatitis which can be complicated by organ failure and local complications such as pancreatic or peripancreatic necrosis[2-4]. Approximately, one third of these patients will develop infection of the necrosis which carries significant morbidity and mortality and will necessitate intervention[5,6].

Historically, open necrosectomy with debridement and post-operative lavage has been the treatment of choice[7]. In the last decade, the surgical step up-approach using a percutaneously inserted drain combined with minimally invasive necrosectomy has become increasingly popular and replaced open surgery as the standard approach[8,9]. As an alternative to surgery, endoscopic procedures for debridement of pancreatic necrosis have become increasingly popular as they offer significantly lower morbidity and mortality rates[10-14]. The endoscopic procedure can also be performed in a step-up approach only to be followed by surgical necrosectomy if endoscopic does not result in clinical improvement. However, there is no evidence to favor any of the surgical, minimally invasive, or endoscopic procedures as the better treatment of severe acute pancreatitis in terms of quality of life.

Traditionally, the outcome of different treatment strategies was determined only in terms of cure, morbidity and mortality[15]. However, in the era of patient-centered medicine, the health-related quality of life (HR-QoL) also needs to be considered[15]. HR-QoL is defined as the perceived physical and mental health of an individual over time. Several studies have investigated the effect of severe acute pancreatitis on HR-QoL and provided some contradictory results[16-22]. Hochman *et al*[19] as well as

Symersky *et al*[20] reported the HR-QoL of patients with SAP was significantly impaired. On the other hand, Soran *et al*[18] and Halonen *et al*[23] stated that patients treated for SAP returned to normal activities. The number of studies that examined HR-QoL of patients with SAP who underwent necrosectomy either surgically or endoscopically is very limited. The aim of this systematic review was to identify and critically appraise the available studies evaluating HR-QoL in patients who underwent either surgical or endoscopic necrosectomy for SAP with necrosis.

MATERIALS AND METHODS

Search strategy

A search for all relevant literature was performed on PubMed, Google™ Scholar, the Cochrane Library and MEDLINE databases in September 2021. The complete search strategy can be found in the Supplementary material. The search was performed without restrictions for date but was limited for full-text articles only. Due to the limited resources available, the search was also restricted to articles available in the English language. Studies investigating HR-QoL in patients with chronic pancreatitis as well as review articles, case reports, guidelines, protocols and abstracts were excluded.

Studies identified through the search strategy were initially assessed for inclusion by the title and abstract and subsequently by full text review (EP). Studies were included when the outcome measure of HR-QoL was either a primary or secondary endpoint. Only studies reporting on adult patients who underwent necrosectomy for severe acute pancreatitis were included. Duplicate studies and populations were cross-referenced and removed. The bibliography of the included studies was also reviewed. Figure 1 demonstrates the preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram[24].

Data extraction

Data were extracted by two independent reviewers (CV and EP) from the included studies with discrepancies resolved by a third (SP) reviewer. Data were collected on the details of each study (authors, year, level of evidence, study type, number of centres involved and country), patient characteristics within each study (sample size, diagnosis, mean age and gender), and HR-QoL details (QoL instruments used, scoring methodology, type of intervention, response and follow-up).

Risk of bias

To assess bias (EP and CV) in the included randomized trials The Cochrane risk of bias tool for randomized control trials (RoB 2.0)[25] was used which focuses upon random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). The risk of bias for the included observational studies was performed using the Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool[26]. This tool focuses upon confounding factors (confounding bias), selection bias, classification of interventions (classification bias), deviation from the intended interventions (performance bias), incomplete outcome data (attrition bias), blinding of outcome assessment (detection bias) and selective reporting (reporting bias). Each study was ranked as low, moderate or high risk of bias based on these criteria (Tables 1 and 2).

RESULTS

Overall, eleven studies were included of which most were from European centres (n = 7)[17,27-32]. Three studies were conducted in American centres[11,16,33] and one in Asia[34]. The studies were undertaken between 1993 and 2020 including an overall number of 756 patients. Three studies were randomized trials[11,28,30], four were prospective cohort studies[17,29,31,32], and four were retrospective cohort studies with prospective follow-up[16,27,33,34]. Only four studies compared surgical intervention to endoscopic intervention[11,27,28,34], while five studies investigated surgical approaches[16,17,29,30,32], and one study investigated endoscopic intervention alone[33]. Most studies were of cohorts with confirmed or suspected infected pancreatic or peripancreatic necrosis requiring intervention. Various metrics of HR-QoL were employed including Short Form (SF)-36[11,16,17,30,33-35], and EuroQol (EQ-5D)[28,30]. Time of administration of HR-QoL tools were variable ranging from 3 to 139 months. Other studies tended to use less known or custom, unvalidated measures of quality of life, limiting between study comparability[27,29,31]. Characteristics of the included studies are summarized in Table 3. A meta-analysis of the included studies was not possible because the populations, interventions, study designs, and outcomes reported varied significantly between studies.

Table 1 Risk of Bias assessment [risk of bias assessment using the Revised Cochrane risk-of-bias for randomised trials (RoB 2.0)]

Ref.	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Bang *et al*[11]	+	+	-	?	+	+	-
van Brunschot *et al*[28]	+	+	-	+	+	+	-
Hollemans *et al*[30]	+	-	-	-	+	+	-

Risk of bias assessment: +: Low; ?: Unclear; -: High.

Table 2 Risk of Bias assessment [risk of bias assessment using the Revised Cochrane risk-of-bias for randomised trials (RoB 2.0)]

Ref.	Confounding	Selection bias	Bias in classification of interventions	Bias due to deviation from intended interventions	Incomplete outcome data	Blinding of outcome assessment	Selective reporting	Other bias
Seifert *et al*[27]	-	-	+	+	+	-	+	-
Smith *et al*[33]	+	+	?	?	-	-	+	-
Cinquepalmi *et al*[17]	?	+	+	+	-	-	+	-
Fenton-Lee *et al*[29]	+	-	?	+	+	-	-	-
Kriwanek *et al* [32]	?	?	-	?	+	-	+	-
Reszetow *et al* [31]	+	?	+	+	+	-	+	-
Broome *et al* [16]	-	?	+	-	-	-	+	-
Tu *et al*[34]	?	+	?	+	+	-	+	-

Risk of bias assessment: +: Low; ?: Unclear; -: High.

Quality of life

Four studies compared HR-QoL between patients who underwent endoscopic and surgical interventions of which two were randomized trials[11,28] and two were retrospective cohorts[27,34]. In Bang *et al*[11]'s randomized trial 34 patients underwent endoscopic necrosectomy and 32 patients underwent minimally invasive surgical necrosectomy for necrotizing pancreatitis. It was reported that the physical component scores for the endoscopic treatment group were significantly improved at 3 months compared to the surgical treatment group (P = 0.39)[11]. In terms of quality adjusted life-years (QALYs) per patient, Bang *et al* reported that QALY gained for endoscopy was 0.452 (BCa 95%CI, 0.434-0.472) compared with 0.450 (BCa 95%CI, 0.427-0.468) for surgery, which translates to a mean difference (MD) of -0.002 (95%CI, 0.029-0.025)[11]. Similarly in van Brunschot *et al*[28]'s randomized trial, the QALY gained for endoscopy was 0.452 (BCa 95%CI, 0.434-0.472) compared with 0.450 (BCa 95%CI, 0.427-0.468) for surgery; with a MD of -0.002 (95%CI, 0.029-0.025).

In the GEPARD Study, 75 patients with pancreatic or peripancreatic necrosis were successfully treated endoscopically[27]. Forty-eight of these patients also showed radiological success as there was no evidence of residual necrosis or cyst on the day of discharge[27]. Eleven of those 75 patients had recurrent pancreatic necrosis, 1 patient had a pancreatitis-related death and 6 non-pancreatitis related deaths at long-term follow-up[27]. This was compared to 18 patients who failed endoscopic therapy, of whom 7 patients died secondary to pancreatitis and 11 progressed to surgery[27]. Of those that progressed to surgery, 8 were successful and 3 had recurrences of pancreatic necrosis[27]. At a mean follow-up of 50 months (range 50-96 months) among 68 patients who underwent successful endoscopic therapy and at a mean follow-up of 53 months (range (15-93 months) among 11 patients that successful surgical treatment; 32 (47%) *vs* 4 (46%) were still working, 31 (46%) *vs* 6 (55%) were retired, and only 5 (7%) *vs* 1 (9%) retired due to disease[27]. A higher proportion of patients reported difficulties with

Table 3 Study characteristics

Ref.	Country	Hospital	Study design	Study interval	Treatment	Patient cohort	Relevant patients	Patients in study	Questionnaire	Assessment times
Broome *et al* [16], 1996	USA	Duke University of Medical Centre	Retrospective with prospective follow-up	1988 to 1994	Surgery (operative debridement of necrosis)	Pancreatic necrosis	40 surgically managed patients with pancreatic necrosis	40	SF-36	Average follow-up 51 mo
Fenton-Lee *et al*[29], 1993	UK	Greater Glasgow Health Board	Prospective	April 1991 to March 1992	Surgery (required operative intervention); 9/10 also received endoscopic procedures	Pancreatic necrosis	10; 10 operative intervention, 9/10 also endoscopic intervention	10	Rosser disability and distress index	Admission and follow-up
Kriwanek *et al* [32], 1998	Austria	Rudolfstiftung-Hospital	Prospective	January 1 1988 to June 30 1996	Surgery (open necrosectomy)	Pancreatic necrosis	75; 57 survivors	75 with pancreatic necrosis (72 other sources of intra-abdominal infection)	SF-36	Not stated
Cinquepalmi *et al*[17], 2006	Italy	Not reported	Prospective	1990 to 2005	Surgery (sequential surgical debridement)	Infected pancreatic necrosis	35; all received sequential surgical debridement	35	SF-36	Not reported
Reszetow *et al* [31], 2007	Poland	Medical University of Gdańsk	Prospective	January 1993 to December 1999	Surgery (Bradley procedure)	Infected pancreatic necrosis	28; 44 (16.1%) of 274 patients with acute pancreatitis; 35/44 (63.4%) survivors for follow-up; 5 excluded	44	Functional Assessment of Chronic Illness Therapy scale	24-96 mo
Seifert *et al* [27], 2009	Germany	6 centres	Retrospective with prospective follow-up	1999 to 2005, follow-up 2004 to 2008	Endoscopy *vs* surgery	Infected pancreatic necrosis	93; 75 endoscopic; 18 failed, 11 surgery	93	Study-specific tool	Up to 24 mo
van Brunschot *et al*[28], 2017	Netherlands	19 centres	Randomized trial	September 20 2011 to January 29 2015	Endoscopy *vs* surgery	Confirmed or suspected infected pancreatic or peripancreatic necrosis.	98; 51 endoscopic and 47 surgical	98	EQ-5D-3L	3 and 6 mo
Hollemans *et al*[30], 2019	Netherlands		Randomized trial	November 2005 to October 2008	Surgery (step-up approach (primary percutaneous catheter drainage, followed by, if necessary, minimally invasive retroperitneal necrosectomy) *vs* open necrosectomy	Confirmed or suspected infected pancreatic necrosis.	60; 28/43 step-up approach (8 died), 32/45 open necrosectomy (7 died)	88	SF-36 and EuroQol	3, 6, and 12 mo after discharge
Smith *et al* [33], 2019	USA	Barnes-Jewish Hospital/Washington	Retrospective with	January 2006 to May 2016	Endoscopy	Walled off necrosis	41 (returned QoL questionnaires)	98	SF-36	Mean 37.4 (range 1-139)

		University School of Medicine	prospective follow-up							mo
Bang *et al*[11], 2020	USA	Florida Hospital	Randomized trial	May 12 2014 to March 24 2017	Endoscopy *vs* surgery	Confirmed or suspected infected pancreatic or peripancreatic necrosis.	66; 34 endoscopic and 32 surgery	66	SF-36	3 and 6 mo
Tu *et al*[34], 2020	China	Jinling Hospital, Medical School of Nanjing University	Retrospective with prospective follow-up	January 2000 to February 2015	Surgery (open necrosectomy) *vs* minimally invasive drainage	Infected pancreatic necrosis	109; 101 included in analysis (61 minimally invasive drainage, 40 open necrosectomy)	109	SF-36	Not stated

carrying heavier loads (36% *vs* 28%), walking around the block (27% *vs* 10%), leaving the house (9% *vs* 7%) who underwent surgical compared to endoscopic therapy[27]. After successful endoscopic necrosectomy more patients had to change their diet (62% *vs* 36%) compared to surgical intervention [27]. On self-assessment those that underwent initial successful endoscopic therapy had improved physical scores (2.47 range 0-10) and quality of life (2.35 range 0-10) compared to those that had surgery after failed endoscopic therapy (physical condition 3.82 range 0-10; quality of life 3.54 range 0-10)[27].

Tu *et al*[34] reports a similar cohort of 101 patients with infected pancreatic necrosis of which 61 underwent minimally invasive drainage (which included percutaneous catheter drainage, negative pressure irrigation or endoscopic necrosectomy) and 40 patients that underwent open necrosectomy. The overall quality of life score was significantly higher in the cohort of infected necrosis patients who underwent minimally invasive drainage compared to open necrosectomy (mean 125 ± 13 *vs* 116 ± 17, P = 0.005)[34]. The quality-of-life domains measured by the SF-36 were comparable between these groups with respect to physical functioning, physical role, but mental health scores were significantly better in minimally invasive drainage group[34].

In a study that assessed HR-QoL in a cohort of 35 patients who underwent sequential surgical necrosectomy for infected pancreatic necrosis, all patients had an SF-36 > 60%, and 78% had scores > 70%-80% suggesting overall good quality of life[17]. Quality of life was notably poorer amongst those with alcoholic pancreatitis. Similarly, 12/32 were able to return to employment within 6 months[17]. Comparably, in another study, 50/57 (88%) patients who underwent open surgical intervention for pancreatic necrosis also had good quality of life[32]. However, in this same cohort 9 patients (16%) experienced worsened employment status[32]. In Smith *et al*[33]'s cohort of 41 patients who underwent endoscopic management of walled-off necrosis, the mean SF-36 general health score was 56.93 (SD 25.82).

Physical functioning and physical role

In a cohort of 80 patients that underwent endoscopic management of walled-off pancreatic necrosis, of whom 41 responded to an SF-36 questionnaire; the mean SF-36 score for physical functioning was 82.32 (standard deviation (SD) 18.24), and 58.54 (SD 40.93) for physical role[33]. This was comparable to Broome *et al*[16]'s cohort of 40 patients with pancreatic necrosis managed *via* surgical debridement with slightly lower physical functioning and physical role SF-36 scores than age-matched controls. In Kriwanek *et al*[32]'s surgically managed cohort, only 2/57 (4%) of patients experienced deteriorated

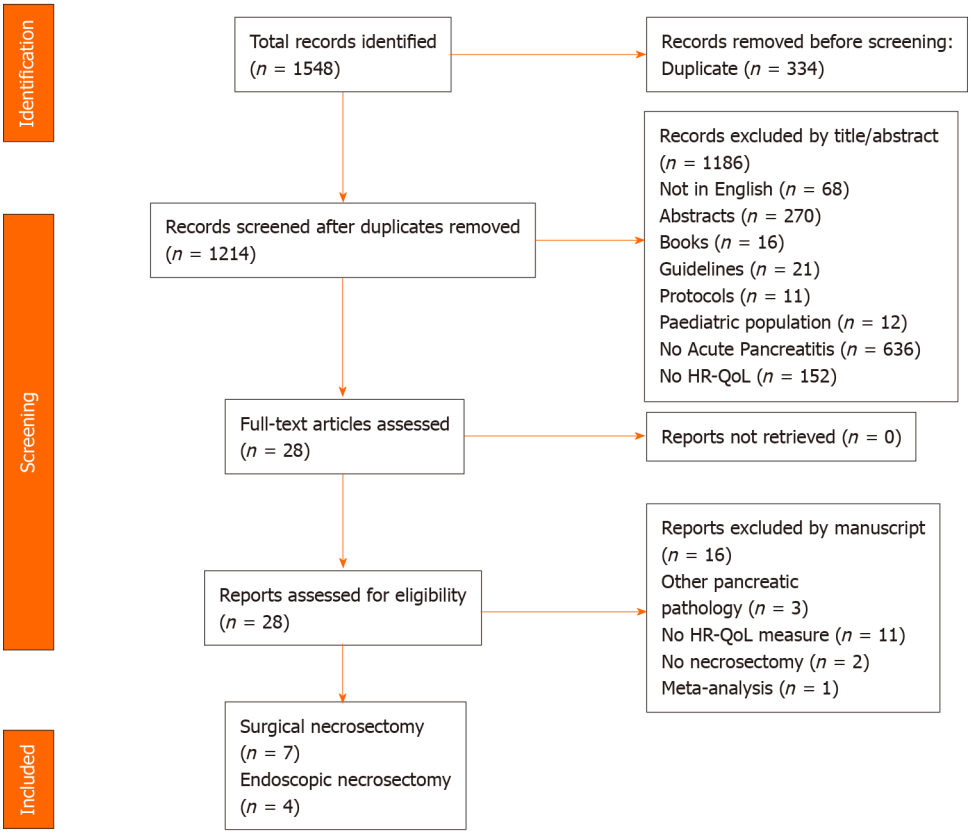

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Figure 1 Preferred reporting items for systematic reviews and meta-analysis PRISMA[24] flow diagram.

functional status as per SF-36. Several studies compared physical component scores of the SF-36 at 3-months and 6-months[11,30,33]. Compared to surgical approach, patients who had endoscopic management of necrotizing pancreatitis had improved physical component scores at discharge, at 3 months, and at 6 months[11,28]. In Holleman *et al*[30]'s randomized trial of step-up approach *vs* straight to open necrosectomy in patients with necrotizing pancreatitis there were no significant differences in the Dutch nor US standard versions of the SF-36 physical health scores between approaches, with scores in both groups being between 42 and 44. These similarities persisted at longer follow-ups[30].

Mental health

Smith *et al*[33] reports in a cohort of 41 patients that underwent endoscopic management of walled of necrosis an SF-36 mental health score of 79.61 (SD 18.52). Only Kriwanek *et al*[32]'s cohort of 57 patients that underwent open surgical intervention for severe intra-abdominal infection and pancreatic necrosis reported on psychosocial functioning and 6 patients (10%) showed depressive mood and 17 (30%) had impaired activity. In contrast to physical function, Bang *et al*[11] found endoscopic intervention compared to surgical intervention was not significantly associated with the mental component score of the SF-36. Broome *et al*[16] found SF-36 mental health scores were comparable between surgically managed patients with necrosis and age-matched controls. Tu *et al*[34]'s cohort also demonstrated improved mental health scores among those who underwent minimally invasive drainage. Similar to the physical functioning, the mental component of the SF-36 questionnaire was similar at baseline and throughout follow-up between step-up approaches and open necrosectomy approaches to necrotizing pancreatitis[30].

Pain

Smith *et al*[33] demonstrated an SF-36 mean bodily pain score of 75.54 (SD 22.78) after endoscopic management of walled-off pancreatic necrosis. This was very comparable to a similar cohort of 40 patients managed with surgical debridement, which in turn was found to be similar to age-matched controls[16]. These findings of equivalence regarding pain between endoscopic and surgical management was further corroborated by Tu *et al*[34]. In another study, 43/57 (75%) patients who underwent open surgical intervention for pancreatic necrosis showed no pain[32].

Other domains of quality of life

Smith *et al*[33]'s cohort of 41 patients with follow-up SF-36 questionnaires after endoscopic management of walled off necrosis reported on the separate domains of the SF-36 HR-QoL measure. Patients' mean vitality scores were 56.83 (SD 23.89), social function scores were 83.84 (SD 20.96), and emotional role scores were 82.30 (SD 34.20). Vitality, social functioning, and emotional role SF-36 scores measured by Smith *et al*[33], were comparable to the scores reported in Broome *et al*[16]' cohort of surgically managed patients with pancreatic necrosis. Tu *et al*[34] was the only remaining cohort which compared these SF-36 domains between surgically managed and endoscopically (minimally invasive drainage) managed patients. It was reported that both social and emotional role functioning were significantly better in the minimally invasive group of patients[34].

Smith *et al*[33] reports that pancreatic exocrine insufficiency (PEI) was the only factor predictive of lower SF-36 scores; and this was true for both the mental and physical components scores. This translated to lower physical role, vitality, emotional role, and mental health scores if patients had PEI [33]. In a randomized trial comparing step-up approach *vs* open necrosectomy for management of necrotizing pancreatitis, they found both approaches were comparable in terms of quality of life[30]. However, quality of life was lower if patients reported abdominal pain, and they did not find PEI (nor pancreatic endocrine function) to affect this[30]. In Cinquepalmi *et al*[17]'s cohort of patients with infected pancreatic necrosis managed with sequential surgical debridement, alcoholic etiology was the only factor associated with poorer SF-36 scores. In contrast, in Reszetow *et al*[31]'s cohort of 24 patients treated with the Bradley procedure for infected pancreatic necrosis, there was no difference in quality of life between those with biliary and alcoholic etiologies.

DISCUSSION

The debridement of pancreatic necrosis remains very challenging for both patients and clinicians as it can have a significant impact on HR-QOL[36,37]. To the best of our knowledge this is the first systematic review to assess HR-QoL following surgical or endoscopic necrosectomy in patients with SAP. Despite the advancements in treatment strategies and the various as well as fundamentally different techniques of necrosectomy, the published data on HR-QoL following each procedure is very limited.

The present review included 11 studies of which 3 were randomized trials[11,28,30] and only four studies compared surgical intervention to endoscopic intervention[11,27,28]. In the overall quality of life following endoscopic intervention *vs* surgical intervention, Bang *et al*[11] reported significantly improved physical component scores for the endoscopic treatment group at the 3-mo follow-up. The authors attributed this to factors such as the shorter duration of the endoscopic procedure, faster resolution of SIRS, fewer disease-related adverse events and shorter length of stay to intensive care unit [11,14,38,39]. In a similar way, patients who were managed endoscopically had improved physical component scores at discharge, at 3 mo, and at 6 mo, whereas Kriwanek *et al*[32] reported that a small number of patients experienced deteriorated functional status following surgical necrosectomy[11,32]. In contrary to Bang *et al*[11], Seifert *et al*[27] stated that less patients reported difficulties in carrying heavy loads, walking around the block or needed to modify their diet following surgical necrosectomy. However, employment status was slightly better in the group of patients who were treated endoscopically[27]. In terms of HR-QoL between patients who underwent open necrosectomy and minimally invasive necrosectomy of the necrotic parenchyma, Tu *et al*[34] reported a significantly better total quality of life as well as vitality and mental health scores following minimally invasive necrosectomy. On the other hand, there was no difference in the physical functioning and bodily pain scores between the two groups of patients. The authors stated that minimally invasive necrosectomy involved a series of procedures that included endoscopic necrosectomy *via* a tract between the stomach and the cavity containing the necrotic parenchyma[34]. The reported results were attributed to pancreatic complications that the open necrosectomy group of patients suffered from[34].

In both randomized trials by Bang *et al*[11] and van Brunschot *et al*[28], the QALY gained following endoscopic necrosectomy was very similar to that following surgical necrosectomy. In terms of mental health, Bang *et al*[11] did not demonstrate any difference in the mental health component of the SF-36 between patients who underwent surgical or endoscopic intervention. However, Kriwanek *et al*[32] reported that 10% of the patients had depressive mood following surgical necrosectomy. With regards to other elements of quality of life, the vitality, social and emotional scores were very good following endoscopic necrosectomy indicating that most patients recovered fully without lasting effects[33]. Patients following open necrosectomy were found to have no pain[32].

Based on this review it is difficult to assess which type of intervention offers the best HR-QoL in patients with severe acute pancreatitis. At present, the strongest evidence has been published by Bang *et al*[11] and favors endoscopic necrosectomy as the treatment of choice. However, all three randomized trials included in this review as well the rest of the included studies were underpowered. Moreover, the lumen apposing metal stents were introduced to clinical practice while the studies by Bang *et al*[11] and Smith *et al*[33] were in progress. Even though this technique was used in some of the patients, it

contributed to the heterogenicity of different endoprostheses that were used. Therefore, more comparative and adequately powered studies are still needed to accurately assess the quality of life following each technique.

None of the included studies assessed the quality of life of the patients while they were hospitalized and therefore the immediate effects of each approach for pancreatic debridement remain unknown. Also, five of the included studies assessed the short-term effect (< 12 mo) and only two studies the long-term effect (> 24 months) while three studies have not stated the intervals or the duration of follow-up. Therefore, even though the SF-36 was designed to primarily assess the long- term effects of a chronic condition[40], the long-term effects of each method of debridement remain grossly unknown.

The SF-36 questionnaire may be a good tool to evaluate HR-QoL and demonstrate the presence of significant changes, but subtle changes might require a different assessment tool to be appreciated. However, other available HR-QoL assessment tools have been compared with the SF-36 and they do not seem to be more accurate[41]. In the era of patient-centered medicine, HR-QoL is regarded as one of cornerstones of the "goal-oriented patient care outcomes" concept[15]. Interestingly, there was significant inconsistency in the use of HR-QoL assessment tools in the included studies. Six out of 10 studies used the SF-36 tool whereas the rest four used either a different or a study-specific tool. This inconsistency made it impossible to safely compare the reported results from different studies and accurately extract outcomes on which treatment approach offers the best outcome. To the best of our knowledge there is no published guidance in the field of pancreatic surgery that recommends a specific tool for HR-QoL assessment. Therefore, the creation of a new tool to evaluate patient reported HR-QoL outcome in patients with pancreatic pathology or even more specifically for acute pancreatitis will deliver a more reliable assessment of different treatment modalities and how they affect the HR-QoL in the sort-, medium- and long-term follow-up period.

The present systematic review has several limitations. The majority of the included studies were observational in nature which might have introduced bias due to confounding. It would be useful if future randomized trials were designed in such a way that HR-QoL was one of the study outcomes. Moreover, the quantitative analysis was challenging to perform due to the various HR-QoL metrics as well as the different timing of administration of the different tools that were employed in the included studies. As mentioned earlier, the SF-36 was originally conceived to evaluate HR-QoL in chronic conditions over a long-term follow-up while three studies in this review have used it to assess short-term follow-up in an acute condition. Another significant limitation of this review was the heterogeneity of the patients among the included studies both in terms of age and severity of the condition as well as the cause of pancreatitis.

CONCLUSION

This systematic review would indicate that the endoscopic approach should be the preferred method for pancreatic necrosectomy. However, more randomized trials in patients with severe acute pancreatitis are needed with HR-QoL as primary endpoint. The goal is to achieve a person-centered coordinated care; through patient reported experience and outcome measures. These instruments are being reported with increasing frequency in the recent years for their ability to bridge the gap between the perceptions of the clinician and patients. This information is then used to adjust treatment and care and to achieve better results, enhance adherence, increase patient satisfaction & quality of life. Finally, it would be useful to create a disease specific HR-QoL assessment tool for acute pancreatitis that will allow comparison of different management options and how they impact the HR-QoL.

ARTICLE HIGHLIGHTS

Research background

Treatment for severe acute pancreatitis (SAP) can significantly affect health related quality of life (HR-QoL). However, the effects of different treatment strategies such as surgical, minimally invasive or endoscopic necrosectomy, on HR-QoL remain poorly investigated. Therefore, there is no evidence to favor any of the existing approaches as the better treatment of SAP in terms of quality of life. To the best of our knowledge this is the first systematic review to assess HR-QoL following pancreatic necrosectomy in patients with SAP.

Research motivation

Traditionally, open necrosectomy has been the standard approach for patients with SAP and necrosis of pancreatic parenchyma. This was followed by the introduction of surgical step up-approach combined with minimally invasive necrosectomy as the treatment of choice. More recently, endoscopic necrosectomy has gained popularity as it offers significantly lower morbidity and mortality rates. However, in the era of patient-centered medicine, HR-QoL also needs to be considered. Unfortunately,

there is no clear evidence to favor any of these procedures as the better treatment of SAP in terms of quality of life.

Research objectives

The objective of this study was to critically appraise the published evidence on HR-QoL in patients with SAP who underwent surgical or endoscopic necrosectomy.

Research methods

A literature search was performed on several databases for studies that examined the HR-QOL following necrosectomy in adult patients with SAP. Studies published in English were excluded due to limited resources. Data were collected on the details of each study, patient characteristics as well as HR-QoL. The Cochrane risk of bias tool for randomized control trials (RoB 2.0) was used to assess bias in the included randomized studies whereas the Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) was used to asses bias in the included observational studies.

Research results

Eleven studies evaluated HR-QoL following necrosectomy including 756 patients. Three studies were randomized trials and eight were cohort studies. One randomized trial and one cohort study demonstrated significantly improved physical scores at three months in patients who underwent endoscopic necrosectomy compared to surgical necrosectomy. In the only study that examined patients following endoscopic necrosectomy, the HR-QoL was also very good. Two randomized trials and one cohort study investigated the quality adjusted life years suggesting that endoscopic and surgical necrosectomy were comparable in cost effectiveness. When open necrosectomy was compared with minimally invasive approaches, patients who underwent the later reported better overall quality of life, vitality and mental health.

Research conclusions

This study would suggest that the endoscopic approach should be the preferred method for pancreatic necrosectomy as it might offer better HR-QoL. However, more randomized trials powered to detect differences in HR-QoL are still required.

Research perspectives

Future research should aim to provide the tools for a person-centered coordinated care through a patient reported experience and outcome measures. This will improve results, adherence, patient satisfaction and quality of life. It is also important to create a disease specific HR-QoL questionnaire for acute pancreatitis to allow evaluation of different management strategies and the impact they have on HR-QoL.

FOOTNOTES

Author contributions: Psaltis E, Varghese C, Pandanaboyana S and Nayar M designed the research study; Psaltis E and Varghese C performed the research; Psaltis E and Varghese C analyzed the data and wrote the manuscript; Pandanaboyana S and Nayar M had the overall supervision of the study; all authors have read and approved the final manuscript.

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CASE REPORT

Solitary pancreatic metastasis from squamous cell lung carcinoma: A case report and review of literature

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Abstract

BACKGROUND

Pancreatic metastases from squamous cell lung carcinoma (SCLC) are unusual. These lesions are often asymptomatic and detected incidentally or during follow-up investigations, occasionally several years after removal of the primary tumor.

CASE SUMMARY

A 56-year-old male with SCLC developed jaundice 1 mo after the cancer diagnosis. An abdominal computed tomography (CT) scan showed a mass in the pancreatic head with distention of both intra- and extrahepatic biliary ducts. Endoscopic retrograde cholangiopancreatography and sphincterotomy were performed first, culminating with plastic biliary stent placement. Cytological examination of the pancreatic mass sample collected by fine-needle aspiration (FNA) under endoscopic ultrasound (EUS) guidance revealed the presence of malignant cells compatible with well-differentiated squamous cell carcinoma. After liver function normalized, chemotherapy was initiated with carboplatin and paclitaxel; however, 4 d later, the patient presented dysphagia. Cervico-thoraco-abdominal CT showed tracheoesophageal fistula and stent migration. After replacement with a 10 cm/10 mm uncovered metallic biliary stent and treatment

of the tracheoesophageal fistula with a fully covered esophageal stent, the patient was able to start oral feeding progressively. He died 9 mo after the initial diagnosis.

CONCLUSION
The diagnosis of pancreatic metastasis from SCLC is challenging for clinicians. EUS-FNA is the primary exam for confirmatory diagnosis.

Key Words: Squamous cell lung carcinoma; Pancreatic metastasis; Jaundice; Esotracheal fistula; Ultrasound endoscopy; Case report

Core Tip: The pancreatic metastasis of squamous lung carcinoma is a rare disease. There are a few cases in the literature that discuss the modality of diagnosis and the treatment of pancreatic metastasis. In this manuscript, we report our experience in the management of this case and the malignant tracheoesophageal fistula as a rare complication of squamous lung carcinoma.

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INTRODUCTION

Pancreatic tumors generally have a poor prognosis, and pancreatic cancer ranks as the fourth deadliest type of cancer among men and women[1]. Pancreatic metastases are rare[2]. Their prevalence is estimated at approximately 1%-5%[3]. Renal, lung, colorectal and breast tumors are the main primary tumor sites responsible for pancreatic metastases[2]. We report a case of squamous cell lung carcinoma with pancreatic metastasis in a 56-year-old male patient.

CASE PRESENTATION

Chief complaints

A 56-year-old male presented to the emergency room with complaints of cholestatic jaundice associated with pancreatic epigastralgia and deterioration of his general condition.

History of present illness

The patient reported that his symptoms had started 1 mo prior.

History of past illness

Three months before admission to our department, he had been diagnosed with and followed up for a left hilar lung squamous cell carcinoma, which had been discovered by bronchoscopy with transbronchial biopsy of the lung mass.

Personal and family history

The patient self-reported being a 52 pack-year smoker, he had no family history.

Physical examination

The patient had obvious jaundice. The patient was afebrile but had epigastric tenderness.

Laboratory examinations

Blood tests showed a disturbance of liver function based on the following findings: total bilirubin, 5.2 mg/dL (normal range: 0.3-1.9 mg/dL); direct bilirubin, 4.1 mg/dL (normal range: 0-0.3 mg/dL); gamma glutamyl transferase, 1088 UI/L (normal range: 12-64 UI/L); alkaline phosphatase, 450 UI/L (normal range: 40-150 UI/L); aspartate aminotransferase, 102 UI/L (normal range: 5-34 UI/L); alanine aminotransferase, 220 UI/L (normal range: 0-55 UI/L); and carbohydrate antigen (CA) 19-9, 40 U/mL

(normal range: 0-33 U/mL).

Imaging examinations

Computed tomographic scanning revealed a tumoral hilar left process, dilation of the intrahepatic bile duct, 11 mm main bile duct and 4 mm Wirsung duct along with a 33 mm × 45 mm pseudotumoral mass of the pancreatic head (Figure 1A and B).

Endoscopic examinations

Endoscopic retrograde cholangiopancreatography was performed and showed dilation of the main bile duct (16 mm) among a stricture (extending to 25 mm) located under the cystic duct. Minimal sphincterotomy was performed, and a plastic stent (10 Fr/7 cm) was placed (Figure 1C). Good drainage was ensured. Histological examination of cytological brushing showed atypical cells, namely, category II of Papanicolaou. The patient's jaundice regressed following these procedures, and his hepatic function blood parameters improved.

First multidisciplinary expert consultation

A multidisciplinary consultation meeting was held. The clinicians decided to begin chemotherapy for lung squamous cell carcinoma.

Treatment

The patient received carboplatin and 80 mg/m^2 paclitaxel every week; however, the treatment was stopped at the 4th week due to poor therapeutic tolerance.

Outcome

Over the 4-d period after treatment cessation, the patient developed total aphagia associated with dysphonia. He also developed stage 4 New York Heart Association dyspnea and was deemed to be undernourished (nutritional risk index of 64). His performance status was 3. A computed tomography arterial portography scan showed a locally advanced left hilar mass invading the left main bronchus and fistulating into a paraseptal formation with intimate contact within the esophageal wall (Figure 2A). The imaging examination also showed left lobar broncho-alveolitis and a cephalic pancreatic tumor invading the second duodenum and the antropyloric portion with dilation of upstream biliary ducts and no pneumobilia. Esophagogastroduodenoscopy showed a tracheoesophageal fistula located 30 cm from the dental arches that easily crossed (Figure 2B). A biliary stent was observed to partially migrate into the duodenum. EUS showed a 4-cm cephalic pancreatic mass invading the second portion of the duodenum (Figure 3A). Fine-needle (22-G) aspiration of the pancreatic mass was performed and confirmed the presence of a carcinomatous proliferation containing nests and large tumoral polygonal cells with atypical voluminous irregular nuclei surrounded by eosinophils. Focal tumoral necrosis was also present, leading us to conclude that the mass was a well-differentiated keratinizing squamous cell carcinoma. Immunohistochemical examination of the mass showed expression of cytokeratin 5/6 (Figure 3B). On the other hand, the cells did not express TTF1. The final histological report confirmed a poorly differentiated squamous cell lung carcinoma located in the pancreas. To address the migrated biliary stent and to ensure definitive and permanent biliary drainage before treating the tracheoesophageal fistula, endoscopic retrograde cholangiopancreatography was performed first with placement of an uncovered metallic stent measuring 10 cm/10 mm (Figure 4A).

MULTIDISCIPLINARY EXPERT CONSULTATION

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The patient's case was rediscussed in multidisciplinary consultation meetings. The decision was made to retain the diagnosis, and a treatment plan was formulated accordingly (detailed below).

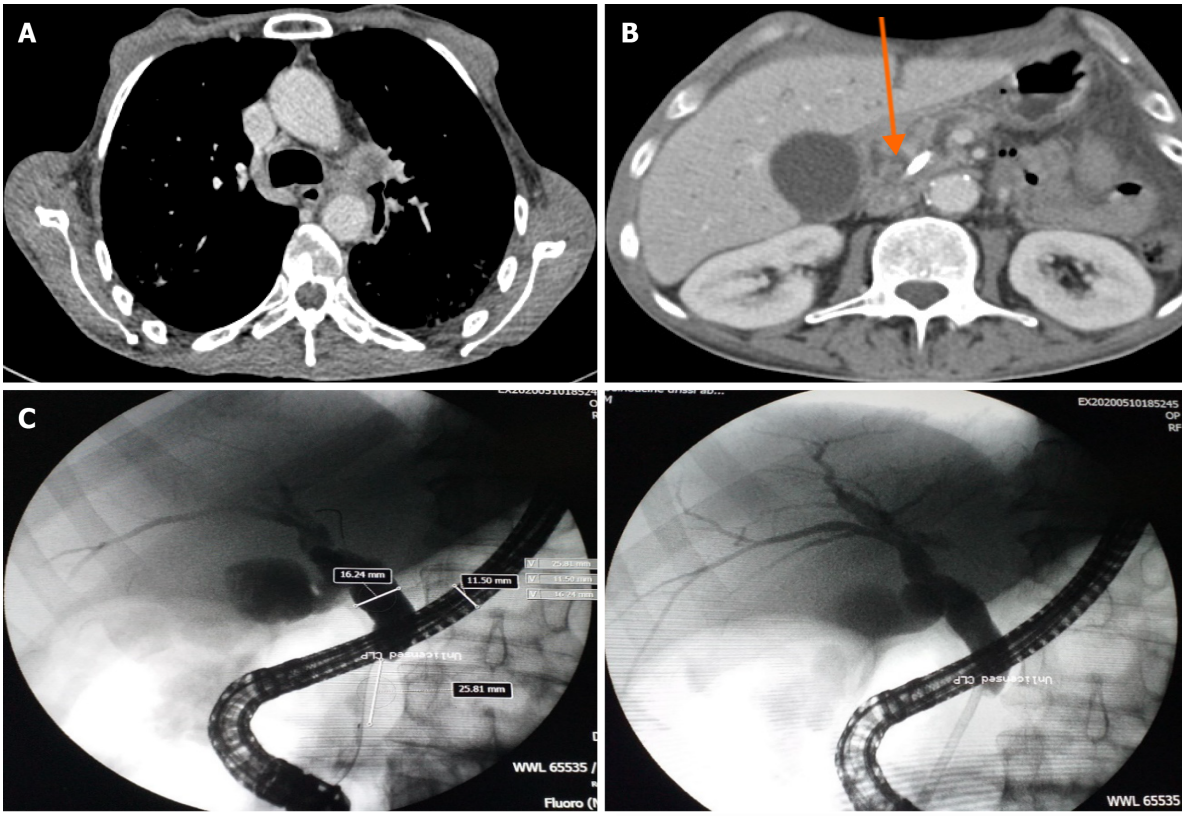

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Figure 1 Imaging and endoscopic images of lung cancer and pancreatic mass. A: Computed tomography scan of the left hilar mass (arrow); B: Computed tomography scan of the mass on the head of the pancreas measuring 4.0 cm × 3.8 cm (arrow); C: Microscopic images showed dilatation of the main bile duct upstream of a very tight stenosis of the cystic duct at 25 mm with insertion of a plastic biliary stent.

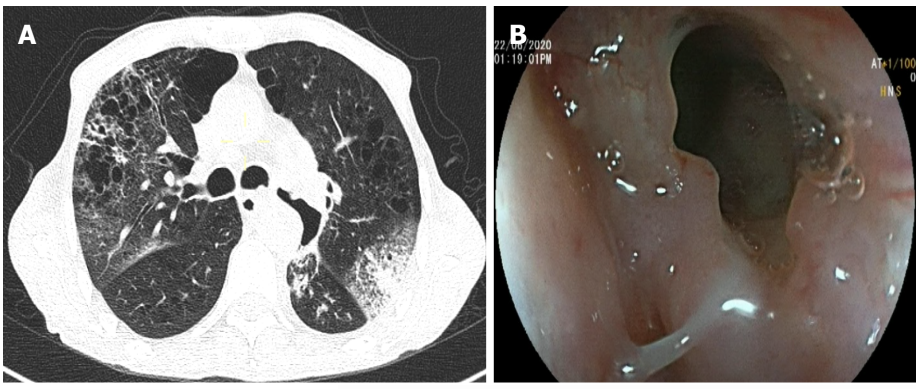

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Figure 2 Tracheoesophageal fistula. A: Computed tomography scan showed left lobar broncho-alveolitis; B: Upper gastrointestinal endoscopy showed a tracheoesophageal fistulae.

FINAL DIAGNOSIS

Pancreatic metastasis of squamous cell lung carcinoma, stage IV.

TREATMENT

A fully covered metallic esophageal stent was placed as a palliative treatment for the tracheoesophageal fistula. Then, a 12-cm stent was placed, the proximal end of which was 24 cm from the dental arches (Figure 4B).

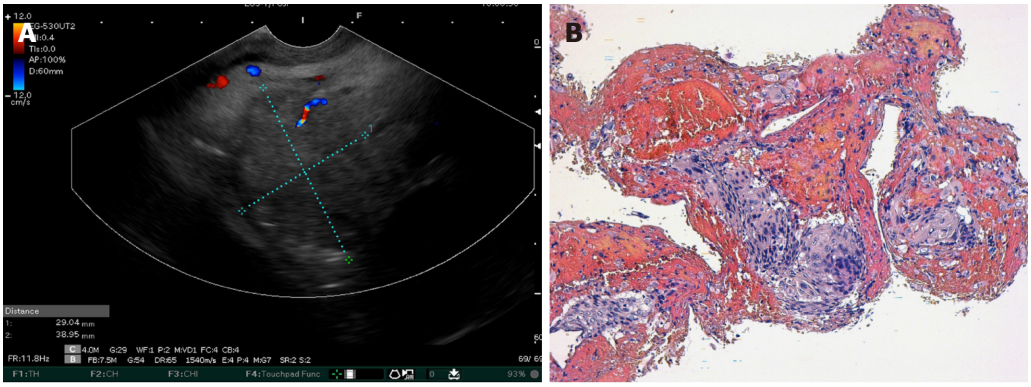

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Figure 3 Images of endoscopic ultrasound and histological analysis of the pancreatic mass. A: Linear endoscopic ultrasound showed a pancreatic head tumor; B: Microphotography showing a proliferation with an easily recognizable squamous differentiation, including apparent intercellular bridges and minimal pleomorphism. Hematoxylin-eosin stain (× 200).

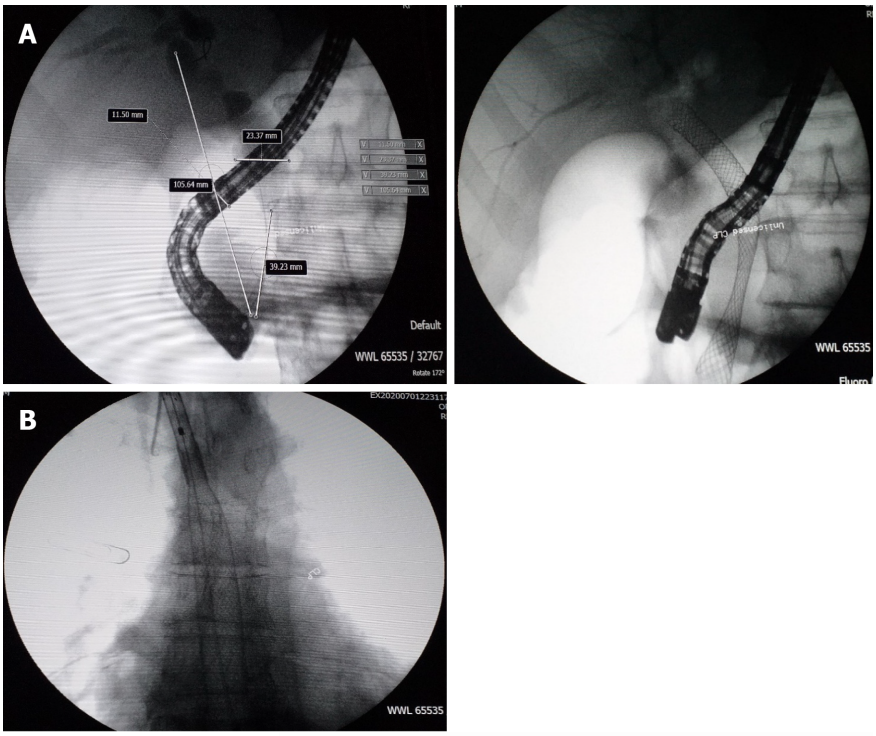

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Figure 4 Placement of metallic biliary stent and esophageal stent. A: An uncovered metallic biliary stent; B: Microscopic image of the fully-covered esophageal stent.

OUTCOME AND FOLLOW-UP

During the following 3 mo, the patient was able to gradually start oral alimentation of a mixed-food diet. However, he lost 5 kg of body weight, and his general state was significantly altered. Thus, palliative chemotherapy was not initiated. Two months later, imaging monitoring using thoracic and abdominal X-rays showed a good position of the esophageal and biliary stents (Figure 5A and 5B), which was confirmed by upper digestive endoscopy (Figure 5C). The patient died 9 mo after the diagnosis.

DISCUSSION

References for this review were identified through searches of the PubMed, Cochrane and Scopus databases using the following Medical Subject Heading terms: (squamous cell lung carcinoma) AND

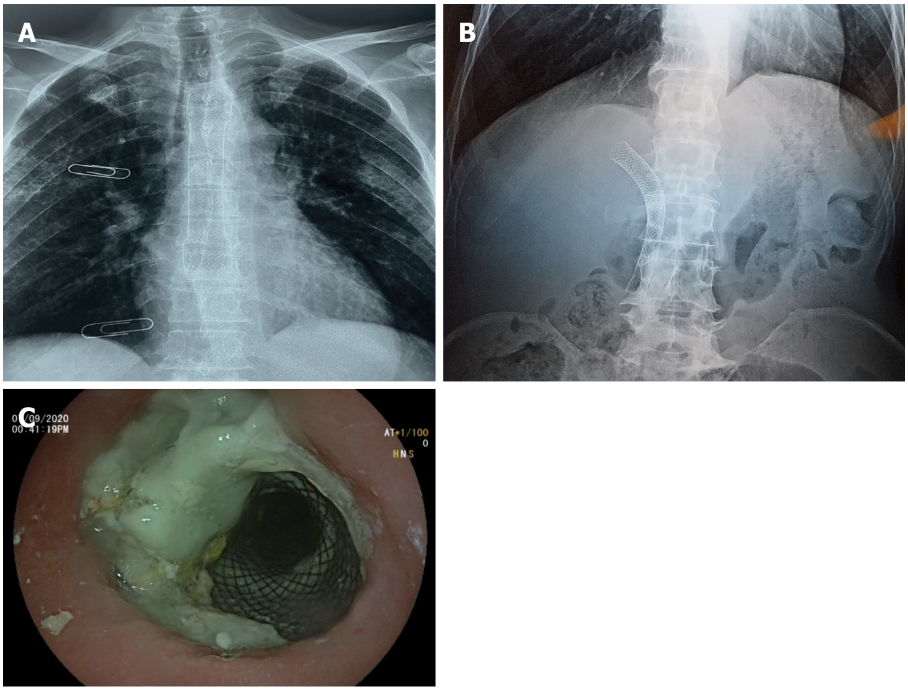

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Figure 5 Chest X-ray and endoscopic images of stents position. A: Position of the esophageal prosthesis; B: Abdomen without preparation showed the position of the biliary metallic stent; C: Covered esophageal stent with food stasis.

(pancreatic metastasis). Only English-language journals were considered, and only full papers were included. A total of 201 studies were initially identified. After reviewing the abstracts, 14 articles were identified with topical relevance (*i.e.*, pancreatic metastasis of a squamous cell lung carcinoma). Reference lists of the selected studies were checked (cross-referenced), but no additional studies were identified (Figure 6). We followed the Preferred Reporting Items for Systematic reviews and Meta-analysis guidelines for this literature review. Only 23 cases of squamous cell lung carcinoma with pancreatic metastasis were reported in the literature at the time of this review. The mean age of the reported patients was 61.5 years, and 92.3% of the patients were male. The most common symptom was jaundice (55.6%) followed by epigastric pain (44.6%). One patient (11.2%) was asymptomatic. Pancreatic metastasis was located in the head of the pancreas in 60% of the patients and was located equally in the body, tail and uncinated process in the remaining patients. EUS benefitted 50% of the patients. Among these patients, 3 patients underwent EUS with fine-needle aspiration (FNA), and 2 patients underwent EUS with fine-needle biopsy (Table 1). The diagnosis of pancreatic metastasis due to squamous cell lung carcinoma was established by EUS in 4 patients, by surgery in 3 patients, by percutaneous FNA of the pancreatic tumor in 1 patient, and upon autopsy in 4 patients. Three patients were treated with biliary drainage. Seven patients received chemotherapy. Two patients received surgical treatment for pancreatic metastasis. The follow-up period for reported patients varied between a few days and 1 year, with the latter noted for 1 patient who was treated with surgery and adjuvant chemotherapy[4] (Table 1).

Lung cancer has a very high rate of morbidity and mortality. In 2018, the World Health Organization reported that lung cancer was responsible for 11.6% of new cancer cases and 18.4% of cancer-related deaths[5]. In total, 20% of non-small-cell lung cancers are classified as squamous cell carcinoma[6]. It has been reported that 40% of cases are already metastatic at diagnosis[7], and the 5-year survival rate is estimated to be only 3.6%[6]. The most common metastatic sites include the bones, lungs, brain, liver and adrenal glands[8]. Pancreatic metastasis is rare, representing only 2% of pancreatic tumors[9]. Primary tumors known to metastasize to the pancreas include renal (25%-48%), lung (15%), breast (8%), colorectal (7%), and bone and melanoma (5%)[9,10]. Through the autopsy of 103 cases of patients with pancreatic metastasis, Nakamura *et al*[11] determined that metastatic dissemination to the pancreas occurred either *via* lymphatic (28%), vascular (27%), lymphatic and vascular (19%) or direct invasion (18%) routes. The authors also assumed that the majority of patients with primary lung cancer (66%) had pancreatic metastasis through vascular dissemination. In another report, the most frequent lung cancer histological type with pancreatic metastasis was cited as small cell carcinoma (10%) followed by large cell carcinoma, squamous cell carcinoma (1.1%), and anaplastic bronchial carcinoma[12]. Frequently, pancreatic metastasis is asymptomatic (> 50%) and discovered accidentally through extension and control assessment[13]. It may be expressed by diverse and nonspecific clinical situations, such as asthenia, weight loss, abdominal pain, jaundice, nausea, or vomiting. Pancreatic metastasis can

Table 1 Summary of the literature review of squamous cell lung carcinoma with pancreatic metastasis

Ref.	Yr	Setting	Number	Age in yr	Sex	Symptoms	Imaging	Endoscopy +/- FNA	Diagnostic means	Treatment	Follow-up	Overall survival	Status at time of publication
Zhou *et al*[29]	2020	China	1	63	M	Epigastric pain with jaundice	Hyperintense mass measuring 4.5 cm in the pancreatic head	No	Surgery of the pancreatic mass	Whipple procedure	UNK	UNK	UNK
Stoupis *et al* [30]	2020	Greece	1	60	F	Fatigue, cough and hemoptysis, loss of appetite and 10-kg weight loss	Increased 2-deoxy-2-[F-18] fluoro-D-glucose uptake in the right lung and pancreatic tail	Yes	EUS-FNB of the pancreatic mass using a 22-gauge needle	7 cycles of anti-PD-L1 antibody pembrolizumab	UNK	UNK	Alive
Wang *et al*[4]	2020	China	1	57	M	Asymptomatic	PET-CT scan showed pancreatic metastasis (1 yr after diagnosis of squamous cell lung carcinoma)	No	Laparoscopic radical pancreatic body tail and splenectomy	4 cycles of gemcitabine (1000 mg/m2) plus cisplatin (65 mg/m2) due to progression of the lung mass and the appearance of a tumor in the head of the pancreas. He received 3 cycles of pembrolizumab (2 mg/kg)	1 yr	21.1 mo	Dead
Ishikawa *et al* [31]	2017	Canada	1	70	M	Abdominal pain and weight loss	3.8 cm hypodense mass in the pancreatic body with lymphadenopathy in the left supraclavicular region and a 3-cm lung mass posterior to the left main stem bronchus	Yes	EUS-FNB of these two lesions with a 25-G needle	Palliative chemotherapy	UNK	UNK	UNK
Fujji *et al*[32]	2015	Japan	1	70	M	High fever and jaundice 6 mo after left lung inferior lobe resection	Low contrast-enhanced mass with relatively clear border and a size of 40 mm × 33 mm in the head of the pancreas	Yes	FNA *via* a transgastric approach with linear EUS	5 cycles of carboplatin plus weekly paclitaxel	226 d	UNK	Dead
Dewanwala *et al*[33]	2012	United States	1	65	M	Dyspnea and recurrent cough	Left hilar mass with an incidental well-defined mass involving the uncinate process of the pancreas measuring 3.7 cm × 2.2 cm	Yes	Pylorus-preserving pancreaticoduodenectomy	Carboplatin plus gemcitabine and completed 5 cycles	17 mo	UNK	Dead
Layfield *et al* [34]	2010	United States	1	UNK	M	UNK	UNK	Yes	EUS + FNA of the pancreatic mass	UNK	UNK	UNK	UNK
Liratzopoulos *et al*[23]	2006	Greece	1	53	M	Jaundice, loss of appetite, nausea and mild abdominal pain	CT scan: carcinoma of the lower lobe of the right lung, a tumor in the pancreatic head measuring 4.0 cm × 4.1 cm × 3.5 cm, dilatation of the biliary tract and multiple enlarged lymph nodes in the cervical area, the mediastinum and the abdomen	No	A percutaneous FNA of the pancreatic tumor under CT guidance	Cholecystojejunostomy + dissection of lymph node near the pancreas	19 d	UNK	Dead

Mesa *et al*[35]	2004	United States	2	UNK	UNK	UNK	Mass in the head of the pancreas measuring 3.6 cm and a lung tumor	Yes	EUS-FNA of the pancreatic mass	UNK	UNK	UNK	UNK
Volkan *et al* [36]	2004	United States	5 of 109 autopsy cases	UNK	UNK	UNK	UNK	UNK	Autopsy	UNK	UNK	UNK	Dead
Tetsuya *et al* [37]	2003	Japan	1	69	M	Jaundice	Lung tumor with hilar and mediastinal lymph node swelling and solitary pancreatic head tumor measuring 3 cm	No	Autopsy	Endoscopic nasobiliary drainage and stent drainage therapy prior to chemotherapy using gemcitabine	4 mo	UNK	Dead
Moazzam *et al* [38]	2002	United States	1	54	M	Anorexia, abdominal pain and jaundice	Mass in right upper lung lobe and mass in the head of pancreas	No	Biopsy of the right upper lobe lung mass	Biliary drainage + carboplatin and paclitaxel	UNK	UNK	Alive: good clinical and radiographic response
Nakamura *et al*[11]	2001	Japan	3 of 103 autopsy cases	UNK	UNK	UNK	UNK	UNK	Autopsy	UNK	UNK	UNK	Dead
Matsukuma *et al*[39]	1997	Japan	3	55	M	UNK	UNK	No	Autopsy	UNK	UNK	UNK	Dead
				64	M								
				58	M								

CT: Computed tomography; EUS: Endoscopic ultrasound; F: Female; FNA: Fine-needle aspiration; FNB: Fine-needle biopsy; M: Male; PD-L1: Programmed death ligand 1; PET: Positron emission tomography; UNK: Unknown.

manifest as upper gastrointestinal bleeding or acute pancreatitis, which were reported in 3 cases[14] and 13 cases[12], respectively. According to Deluzio *et al*[15], 59% of patients with pancreatic metastasis had gastrointestinal symptoms, mostly represented by jaundice and abdominal pain. Jaundice is explained by the obstruction of extrahepatic biliary ducts by pancreatic metastasis, which is essentially observed in small cell lung cancer[16]. The diagnosis of pancreatic metastasis and the differentiation of primary and metastatic tumors represent significant challenges. Pancreatic metastasis shows varied enhancement when imaged. Klein *et al*[17] reported that 76% of pancreatic metastases showed greater vascular enhancement than normal pancreatic parenchyma or primary pancreatic tumors, which is explained by the richness of metastatic vascularization. EUS is the main exam for pancreatic lesions and their locoregional extension. The sensitivity of EUS is estimated at 100% for tumors < 2 cm, whereas the sensitivity values of ultrasound and abdominal scan are 60% and 50%, respectively[16]. A retrospective study by El Hajj *et al*[10] included 49 patients with pancreatic metastasis and found that the lesions were hypoechoic in 80% of patients, hyperechoic in 4% of patients, mixed in 4% of patients, and anechoic in 2% of patients. Regular boundaries were observed in 55% of cases. To confirm the diagnosis, cytological analysis was used in 63% of cases, whereas immunohistochemical analysis was added to the former technique in 33% of these cases. Dewitt *et al*[18] demonstrated that EUS-FNA confirmed the diagnosis of pancreatic metastasis in all patients with a secondary pancreatic tumor. They also deduced that the only ultrasound data that could differentiate between primary and secondary pancreatic tumors involved the

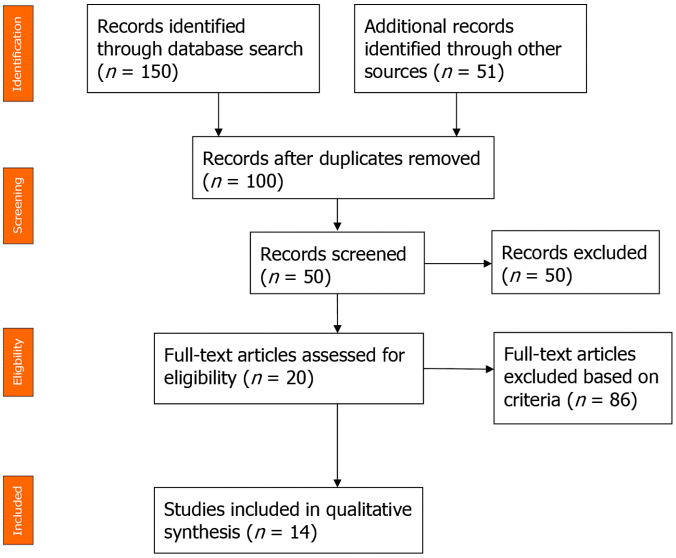

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Figure 6 Flow diagram of the literature review of squamous cell lung carcinoma with pancreatic metastasis.

lesion margins. Margins were well defined when the tumor was secondary (46% *vs* 4%) and irregular in 94% of primary pancreatic tumors (94% *vs* 54%) ($P < 0.0001$). However, no significant differences were noted between primary and metastatic pancreatic tumors regarding tumor number, size, location, or echogenicity parameters. For metastatic lung cancer, therapeutic care consists of palliative chemotherapy and biliary drainage when the tumor compresses the biliary ducts. According to the National Comprehensive Cancer Network guidelines, metastatic squamous cell carcinoma treatment depends on the patient's performance status[19]. These options should be discussed during the multidisciplinary expert consultation. Regimens of pembrolizumab, carboplatin and paclitaxel or pembrolizumab, carboplatin, paclitaxel and albumin are used as the first-line treatment for patients whose performance status is 0 to 1. When the performance status is 2, carboplatin, paclitaxel and albumin or carboplatin and gemcitabine or carboplatin and paclitaxel are the recommended therapeutic options. Our patient had a performance status of 2, indicating that he should be treated with carboplatin and paclitaxel. However, this treatment was stopped due to intolerance. Recently, many scientific publications have discussed the surgical treatment of oligometastatic lung cancer in the pancreas. Kageyama *et al*[3] reported a unique case of a 67-year-old patient who had lung cancer with a pancreatic metastasis that was randomly discovered during follow-up tests 6 years after the primary tumor diagnosis. The patient underwent a distal pancreatectomy and ganglion dissection, which led to survival at 5 years without any recurrence. Ida *et al*[20] showed a longer survival of 8 years in a 70-year-old male patient with metastatic squamous cell lung carcinoma who underwent a total pancreatectomy and a resection of the portal vein. According to a Japanese retrospective study that evaluated global survival in patients receiving a surgical operation for pancreatic metastasis, 6 of the 9 patients survived for more than 23.5 mo. However, patients with longer survival times had pancreatic tumors secondary to renal cancer[21]. Generally, pancreatic metastasis of squamous cell lung carcinoma is discovered at an advanced stage[22], and only 2% of the tumors are resectable[23], revealing why surgical treatment is rarely utilized. Moreover, this case is unusual given the presence of a malignant tracheoesophageal fistula as a rare complication of squamous cell lung carcinoma. Malignant tracheoesophageal or bronchoesophageal fistula develops in 5%-15% of patients with esophageal cancer, and only 0.2% of lung malignancies have been reported to cause esophageal pulmonary fistulae[24]. In patients with prior lung or esophageal cancer, the presence of symptoms, such as dysphagia, recurrent pneumonia or treatment-resistant pneumonia, should raise concern as to whether an underlying fistula is present. If not detected early or left untreated, the fistulae may lead to pneumonitis and lung abscesses that cause sepsis, acute respiratory distress syndrome, and death. In addition, without treatment, the median survival may be 1-6 wk[25]. There is no cure for malignant tracheoesophageal fistulae, and palliative procedures, such as esophageal stenting, esophageal exclusion, esophageal bypass or surgical repair with fistula resection, may prolong survival and provide immediate symptom relief. Based on a comparative study of the survival time and quality of life of patients who received different treatments for tracheoesophageal fistulae, self-expandable stenting did not significantly prolong the survival time of patients but did remarkably improve health-related quality of life[26]. The European Society of Gastrointestinal Endoscopy recommends esophageal self-expandable metallic stent placement as the preferred treatment for sealing malignant tracheoesophageal fistulae[27]. However, the reported success rates of esophageal stent placement vary from 70% to 100%. In addition, some complications may occur,

such as stent migration, bleeding, granulation formation, foreign body sensation, and secondary fistulae, all of which have been reported as late complications of stenting[24]. In our case, the malignant tracheoesophageal fistula was successfully treated by an fully covered esophageal metallic stent. Unfortunately, our patient died 6 mo after the diagnosis of pancreatic metastasis. This was not surprising because stage IV squamous cell lung carcinoma with pancreatic metastasis has a poor prognosis in general with an average reported survival of 8.7 mo after diagnosis[28].

CONCLUSION

Squamous cell lung carcinoma with pancreatic metastasis is rare, and its diagnosis represents a challenge for clinicians. Radiological, endoscopic and anatomopathological methods are needed for an accurate diagnosis. EUS-FNA is the ideal procedure to diagnose pancreatic metastasis. This disease has a poor prognosis because it is generally detected at an advanced stage. Thus, the treatment is typically palliative.

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FOOTNOTES

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Abstract

Gallstone cholangiopancreatitis is a potentially life-threatening pathology which requires quick intervention involving endoscopists, interventional radiologists, anesthesiologists and surgeons in relation to clinical conditions. Treatment possibilities are varied, especially with current progress in advanced endoscopy, interventional radiology, and minimally invasive surgery. The following treatments are available: endoscopic sphincterotomy (ES) with stone extraction followed by laparoscopic cholecystectomy; simultaneous endoscopic stone extraction with laparoscopic cholecystectomy (rendezvous technique); combined laparoscopic cholecystectomy and common bile duct (CBD) exploration; open CBD exploration; ES post-cholecystectomy; percutaneous placement of biliary drains for unstable patients, followed by percutaneous cholangioscopy; and lithotripsy with different approaches, including a laser and balloon dilation of the sphincter of Oddi. Each technique has its strengths and weaknesses, and there is great discussion in the literature on choosing the ideal approach based on the patient's clinical conditions.

Key Words: Cholangiopancreatitis; Common bile duct stones; Endoscopic retrograde cholangiopancreatography; Endoscopic sphincterotomy; Laparoscopic common bile duct exploration; Percutaneous

Core Tip: Urgent biliary decompression represents the treatment of gallstone pancreatitis associated with cholangitis. There are different techniques for common bile duct (CBD) clearance. Endoscopic retrograde cholangiopancreatography is not always feasible, as in the case of poor clinical conditions, large stones, or biliodigestive derivations. We analyzed the different approaches for decompression of the CBD in the case of "cholangiopancreatitis".

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TO THE EDITOR

We read with interest the article by Isogai[1] about the definition of "gallstone cholangiopancreatitis," and the assessments regarding the aetiology and prognosis. Although the study is very well worded, we would like to add a few comments.

We think that it is complex to distinguish, with the only dosage of alanine aminotransferase, between a liver disease or the onset of multi-organ failure and cholangitis associated with pancreatitis[2]. However, the reflections expressed in the document stimulate the research activity to realize diagnostic methods that allow distinguishing "cholangiopancreatitis" from other adverse events that can worsen the clinical course of acute pancreatitis.

Moreover, we would like to integrate the different CBD obstruction management techniques even if this was not the main focus of the article.

Acute pancreatitis complicated by cholangitis due to CBD obstruction must be approached with an urgent decompression of the biliary tract to improve the pathology course. There are different approaches to decompress CBD, such as endoscopic retrograde cholangiopancreatography (ERCP), concerning the clinical conditions, the diameter of the stones, and any previous biliodigestive derivation. Urgent ERCP is recommended in patients with gallstone pancreatitis and concomitant cholangitis. The guidelines suggest that ERCP can improve the course in patients with CBD obstruction even in the absence of cholangitis[3-5].

In the study by Schepers *et al*[6], it appears that urgent ERCP associated with sphincterotomy may help in cholangitis complicating acute pancreatitis or in persistent obstruction of CBD. ERCP results in excellent clearance of CBD; nevertheless, in a certain proportion of patients, it may be necessary to resort to multiple procedures. ERCP associated with sphincterotomy is an aggressive approach which can lead to complications in up to 10% of patients[7,8], including bleeding, cholangitis, pancreatitis, duodenal perforation, and CBD lesions. A previous study showed that ERCP could lead to an increase in respiratory complications[9-13]. Sedation and possible aspiration can lead to respiratory complications in clinically critically ill patients. In the study of Schepers *et al*[6], in the urgent ERCP group there were more intensive care unit admissions.

Our clinical approach to patients with severe clinical conditions, unable to withstand general anesthesia or deep sedation is to subject these patients to percutaneous decompression of the CBD with a drain placed under local anesthesia and possible subsequent clearance of the CBD with the use of percutaneous cholangioscopy and laser.

Percutaneous biliary drainage can also have complications such as infections, and it can become blocked or displaced. However, it allows performing cholangiographies that can evaluate the possible presence of residual stones or the complete clearance of the biliary tract throughout their entire course. Once the patient's clinical condition has been improved, surgery and rendezvous ERCP can be carried out; if endoscopic treatment is not feasible, a laparoscopic exploration of CBD (LCBDE) could be performed.

In the study of Aawsaj *et al*[14] the LCBDE has been used in both elective and emergency contexts. A transcystic approach is preferable whenever possible. It is preferable to perform cholecystectomy during the same hospitalization to avoid recurrent gallstone pancreatitis.

A previous review by Dasari *et al*[15] showed no difference in clearance, morbidity, and mortality between open surgery and ERCP. In the ERCP group there were significantly more retained stones than in the open surgery group (16% *vs* 6%; $P = 0.0002$).

Laparoscopic cholecystectomy (LC) + LCBDE had fewer retained stones (8%) than two-staged pre-operative ERCP plus LC or LC plus post-operative ERCP (14%) (P = not significant). In the study by Ding *et al*[16], there were more recurrent CBD stones in the two-stage group at longer-term follow-up (9.5% *vs* 2.1%; $P = 0.037$). In the endoscopic group, there were more procedures per patient ($P < 0.001$) and most costly espenses ($P = 0.002$).

The study of Bansal *et al*[17] showed a shorter hospital stay in the single-stage group but no differences in major complications between the two groups.

Percutaneous or endoscopic balloon dilation represents a valid alternative to ES. It is simpler, has fewer complications in terms of bleeding and sphincter of Oddi lesions but has a lower performance in CBD clearance than ES[18,19]. In the current era, endoscopic approaches guarantee excellent results in the management of the biliary tract. Surgical management of CBD can be a viable option for patients in good condition with large diameter stones, previous biliodigestive derivations, and in case of failure of the endoscopic approach[20-22]. In addition, laparoscopic treatment can be performed with single anesthesia. Exploration of CBD by intraoperative choledochoscopy and simultaneous biliary clearance in a single time is not very aggressive and safe, with excellent results for treating "gallstone cholangiopancreatitis" and should only be performed in high volume centres with surgeons with proven experience. The laparoscopic management of CBD stones also reduces the average hospital stay, the anesthetic risks associated with two different procedures, and the cost of multiple hospitalizations.

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LETTER TO THE EDITOR

Texture and color enhancement imaging for detecting colorectal adenomas: Good, but not good enough

Ying Wang, Chen-Yu Sun, Lowe Scott, Dan-Dan Wu, Xia Chen

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Abstract

Texture and color enhancement imaging (TXI) has been developed as a novel image-enhancing endoscopy. However, the effectiveness of TXI detecting adenomas is inferior to narrow band imaging. Thus, future studies will need to focus on investigating the feasibility of such combination in clinical settings in order to provide patients with more accurate diagnoses.

Key Words: White light imaging; Texture and color enhancement imaging; Narrow band imaging; Colorectal adenomas

Core Tip: Texture and color enhancement imaging (TXI) is designed to enhance three image factors in white light imaging (texture, brightness, and color) in order to clearly define subtle tissue differences. Latest articles reported that TXI may likely contribute to the detection of early gastric cancer. Notably, the synergistic added value of TXI and near-focus mode was discovered during saline-immersion endoscopic submucosal dissection by improving submucosal space visibility. As the authors put it, the effectiveness of TXI detecting adenomas is inferior to narrow band imaging.

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TO THE EDITOR

With great curiosities, we examined the article "Texture and color enhancement imaging in magnifying endoscopic evaluation of colorectal adenomas" recently published by Toyoshima *et al*[1]. In this study, a total of sixty-one consecutive adenomas with completed white light imaging (WLI), texture and color enhancement imaging (TXI), narrow band imaging (NBI), and chromoendoscopy (CE) were investigated. In the present study, the visibility score for tumor margin of TXI was significantly higher than that of WLI, but lower than that of NBI. Additionally, TXI had a higher visibility score for the vessel as well as surface pattern of the JNET classification than WLI and CE, but a lower visibility score than NBI.

To detect colorectal polyp and gastric cancer, endoscopy with WLI is currently the gold standard. However, the accuracy of WLI for detecting early lesions in both the colorectal and gastric regions is yet to be established[2]. Meanwhile, TXI was proposed as a new image enhancement technology to resolve these drawbacks by Sato[3]. To avoid losing subtle tissue differences, TXI is designed to enhance the three imaging factors in WLI (texture, brightness, and color). According to recent publications, it has been suggested that TXI may likely contribute to the increased detection rate of early gastric cancer[4]. Moreover, a significant synergistic value of TXI and near-focus mode was discovered during endoscopic submucosal dissection performed in saline-immersion by improving the visibility of submucosal spaces [5]. In a study by Nishizawa *et al*[6], WLI, TXI, NBI, and chromoendoscopy were performed on twenty-nine patients with serrated polyps. Similarly, the authors indicated that TXI provided higher degree of clarity in visualization for the detection of serrated, colorectal polyps, as well as sessile serrated lesions.

It is noteworthy that Toyoshima *et al*[1] concluded that the effectiveness of TXI detecting adenomas is inferior to NBI under certain circumstances. Furthermore, TXI could also be combined with other optical image enhancement technology such as NBI, since TXI is implemented entirely in the chain of endoscopic image processing. Finally, it is suggested that future researches should focus on investigating the feasibility of such combination in clinical settings in order to provide patients with more accurate diagnoses.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Disparities in colonoscopy utilization for lower gastrointestinal bleeding in rural *vs* urban settings in the United States

Nagapratap Ganta, Mina Aknouk, Dina Alnabwani, Ivan Nikiforov, Veera Jayasree Latha Bommu, Vraj Patel, Pramil Cheriyath, Christopher S Hollenbeak, Alan Hamza

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Abstract

BACKGROUND

Lower gastrointestinal bleeds (LGIB) is a very common inpatient condition in the United States. Gastrointestinal bleeds have a variety of presentations, from minor bleeding to severe hemorrhage and shock. Although previous studies investigated the efficacy of colonoscopy in hospitalized patients with LGIB, there is limited research that discusses disparities in colonoscopy utilization in patients with LGIB in urban and rural settings.

AIM

To investigate the difference in utilization of colonoscopy in lower gastrointestinal bleeding between patients hospitalized in urban and rural hospitals.

METHODS

This is a retrospective cohort study of 157748 patients using National Inpatient Sample data and the Healthcare Cost and Utilization Project provided by the Agency for Healthcare Research and Quality. It includes patients 18 years and older hospitalized with LGIB admitted between 2010 and 2016. This study does not differentiate between acute and chronic LGIB and both are included in this study. The primary outcome measure of this study was the utilization of colonoscopy among patients in rural and urban hospitals admitted for lower gastrointestinal bleeds; the secondary outcome measures were in-hospital mortality, length of stay, and costs involved in those receiving colonoscopy for LGIB. Statistical analyses were all performed using STATA software. Logistic

regression was used to analyze the utilization of colonoscopy and mortality, and a generalized linear model was used to analyze the length of stay and cost.

RESULTS

Our study found that 37.9% of LGIB patients at rural hospitals compared to approximately 45.1% at urban hospitals received colonoscopy, (OR = 0.730, 95%CI: 0.705-0.7, $P > 0.0001$). After controlling for covariates, colonoscopies were found to have a protective association with lower in-hospital mortality [OR = 0.498, 95%CI: 0.446-0.557, $P < 0.0001$], but a longer length of stay by 0.72 d (95%CI: 0.677-0.759 d, $P < 0.0001$) and approximately $2199 in increased costs.

CONCLUSION

Although there was a lower percentage of LGIB patients that received colonoscopies in rural hospitals compared to urban hospitals, patients in both urban and rural hospitals with LGIB undergoing colonoscopy had decreased in-hospital mortality. In both settings, benefit came at a cost of extended stay, and higher total costs.

Key Words: Lower gastrointestinal bleeding; Rural-urban disparities; Colonoscopy; Utilization of colonoscopy; Length of stay; Inpatient admission costs

Core Tip: Colonoscopy utilization is lower in rural hospitals than in urban hospitals in the United States for all acute and chronic lower gastrointestinal bleeding. Patients in both rural and urban hospitals who present with lower gastrointestinal bleeds that undergo colonoscopy have decreased in-hospital mortality, an extended length of hospital stay, and higher total costs.

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INTRODUCTION

Gastrointestinal (GI) bleeding is the most common cause of hospitalization due to gastrointestinal disease in the United States and is responsible for 2%-4% of hospital mortality[1]. Approximately 30% to 40% of all cases of GI bleeding are from a lower GI source[2]. Over the past decade, there has been a progressive change in GI bleeding patterns that lead to hospitalization, with a clear decreasing trend in upper GI events and a significant increase in lower GI events[3]. Unfortunately, even though lower gastrointestinal bleeding (LGIB) is a common indication for admission to the hospital, it has received relatively little attention in the literature[4]. The estimated hospitalization rate for LGIB is 33-87 per 100000 population[3] with mortality rates of 2%-4% during hospitalization and rebleeding rates of 13%-19% after one year[4] . Diverticular bleeds are the leading cause of LGIB and account for approximately 30%-50% of all cases[5]. In patients 50 years or younger, the leading cause of LGIB is hemorrhoids, which often present as minor bleeding. Increased incidence of LGIB with age is likely secondary to increased diverticulosis and angiodysplasia[1]. Other conditions that are commonly associated with LGIB include angiodysplasia, ischemic colitis, colon cancer/polyps, post-polypectomy bleeding, inflammatory bowel disease, solitary rectal ulcer, radiation colitis/proctitis, and rectal varices[6]. Colonoscopy is a minimally invasive procedure that improves clinical outcomes which include- decreased rebleeding, decreased duration of hospital stay, and decreased need for major surgery[7].

Primary intervention in diagnosing LGIB is receiving a colonoscopy and it is important that the procedure is performed with minimal delay[8]. Currently the large majority of diagnostic and therapeutic procedures in Gastroenterology is the colonoscopy. In 2015, approximately 11.5 million colonoscopies were performed compared to 6.1 million upper endoscopies and a significantly lower rate of flex sigmoidoscopies at 313000 annually[2]. Urgent Golytely preparation and colonoscopy is the most direct and cost effective approach to diagnose hematochezia[7].

Several factors might contribute to rural-urban disparities in utilizing colonoscopy. Major factors may be rural provider distribution and scarcity, challenges that have persisted despite significant attempts by federal and state governments to address them over the last three decades[9]. The increased disparity is also linked to fewer specialist visits and a greater reliance on generalists in rural regions. Therefore,

examining differences in rural hospitals and the benefits of colonoscopy among patients with lower gastrointestinal bleeds can lead to better patient outcomes.

This study is aimed to determine whether there were rural disparities in colonoscopy utilization in hospitalized patients with lower GI bleeding (LGIB) and the benefits of receiving a colonoscopy.

MATERIALS AND METHODS

Study design

This is a retrospective cohort study.

Data source

Data used in this study were from the National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), provided by the Agency for Healthcare Research and Quality (AHRQ). The NIS is the most extensive all-payer administrative discharge data set in the US and contains information on discharges from community hospitals[10]. Cohorts of hospitalized patients can be identified in the NIS using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) codes for the third quarter of 2015 and earlier, and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) codes for the fourth quarter of 2015 and later.

Cohort

This study examined 157748 patients from the United States aged 18 and older in the NIS hospitalized with a principal diagnosis of LGIB between 2010 and 2016. There is no differentiation between acute or chronic bleeding. The algorithm described by Strate *et al*[4] was used to define the cohort. While Strate *et al*[4] defines a cohort of patients with LGIB ICD-9 diagnosis and procedure codes, the general equivalence mappings (GEM) from the Centers for Medicare and Medicaid Services (CMS) were used to extend their algorithm to ICD-10 diagnosis and procedural classification system (PCS) codes[11-13].

Patients with a principal ICD-9 diagnosis code indicating lower gastrointestinal bleeding were included in the cohort, including 562.12 (Diverticulosis of colon with hemorrhage), 562.13 (Diverticulitis of colon with hemorrhage), 569.85 (Angiodysplasia of the intestine with bleeding), 569.3 (Hemorrhage of rectum and anus), 455.2 (Internal hemorrhoids with other complication), 455.5 (External hemorrhoids with further complication) and 455.8 (Unspecified hemorrhoids with other complication). We also included patients with a secondary ICD-9 code that indicated a source of bleeding in the lower gastrointestinal tract (Supplementary material). Furthermore, patients were excluded if the source of bleeding appeared to be in the upper gastrointestinal tract or if they had an ICD-9 procedure code or ICD-10 PCS code suggestive of a surgical procedure in the upper gastrointestinal tract or small intestine. ICD-9 diagnosis and procedure codes were used for inclusion or exclusion criteria, and comparable ICD-10 codes are listed in Supplementary material. Since we have based our study on administrative data obtained from NIS, which is further based purely on ICD codes, we cannot comment with certainty as to the clinical details on why colonoscopy was not done in some patients with LGIB and if any other diagnostics were used. A study based on a medical chart review would be able to better answer the questions related to the final diagnosis or cause of LGIB or why colonoscopy was not done in some patients, and we would definitely want to conduct a study in the future to analyze these details.

The primary outcome of this study was the utilization of colonoscopy. This was identified using a principle or secondary ICD-9 procedure code of 45.23 (colonoscopy) or a principle or secondary ICD-10 PCS code of 0DJD8ZZ (Inspection of Lower Intestinal Tract, Via Natural or Artificial Opening Endoscopic). In addition, three secondary outcomes were studied, including in-hospital mortality, length of stay, and costs. Length of stay was defined as total days from admission to discharge or death. Costs were estimated from the hospital perspective from hospital-level ratios of costs-to-charges. All charges were adjusted to the year 2018 US dollars using the medical care component of the consumer price index.

Covariates

All multivariable analyses controlled for the patient and hospital characteristics. Models controlled for age (18-64, 65-74, 75-84, 85+), sex (male, female), race (white, black, Hispanic, Asian, other), and primary payer (Medicare, Medicaid, commercial, other). We controlled the size of the hospital (small, medium, large) and the teaching status of the hospital. Teaching hospitals have at least one Accreditation Council for Graduate Medical Education (ACGME) approved residency program or are members of the Council of Teaching Hospitals (COTH). Comorbidities were controlled using the Charlson Comorbidity Index, a weighted index of 17 comorbidities[14,15]. Finally, we controlled for the geography of the hospital (rural, urban). Geography was based on the county where the hospital is located. Rural hospitals were identified as those located in counties with a core-based statistical area designated as micropolitan or non-core. This classification of rural-urban is based on the site's zip code.

Statistical analysis

Statistical analyses were designed to determine whether there was a significant association between rural hospital designation and utilization of colonoscopy among patients admitted for gastrointestinal bleeding. In addition, we tested whether patients who received colonoscopy had significantly different rates of in-hospital mortality, length of hospital stay, and hospital costs. Characteristics of patients were compared between those who received care at rural *vs* urban hospitals using *t*-tests for continuous variables and chi-square tests for binary and categorical variables. Utilization of colonoscopy was modeled using logistic regression, controlling for patient and hospital characteristics. Mortality was also modeled using logistic regression. Length of stay and costs were modeled using linear regression, controlling for patient and hospital characteristics. A propensity score analysis matched patients who received care at a rural hospital to those at an urban hospital. Matching was performed using a 1:1 nearest neighbor approach and a caliper restriction of 0.2 times the standard deviation. Statistical analyses were performed using STATA software (version 15, College Station, TX, United States). Statistical significance was defined as $P < 0.05$.

RESULTS

Rates of colonoscopy utilization stratified by rurality are presented in Figure 1. Approximately 37.9% of patients with lower gastrointestinal bleeding received colonoscopy at rural hospitals compared to 45.1% at urban hospitals. Rural hospitals had a consistently lower rate of colonoscopy utilization relative to urban hospitals from 2010 through 2015. The difference was mediated to a large degree in 2016. Also, there was a trend for decreasing colonoscopy utilization in both settings.

As seen in Table 1, patients differed significantly in demographics and comorbidities. However, much of the significance was due to the considerable sample size. For example, patients treated at rural hospitals tended to be slightly older (74.4 years *vs* 73.0 years, $P < 0.0001$), more likely to be female (53.7% *vs* 51.9%, $P < 0.0001$), and significantly more likely to be white (74.6% *vs* 63.9%). Instead of other payers, they were more likely to be insured by Medicare (78.8% *vs* 74.3%). Hospital characteristics also differed significantly. For example, all rural hospitals are non-teaching hospitals, and bed size varies by region and rurality in the NIS[10]. A large hospital in a rural area in the Northeast has 100 or more beds, while a large, urban teaching hospital has 425 or more beds. A large hospital in a rural area in the West has 45 or more beds, while a large, urban teaching hospital has 325 or more beds.

After controlling for other factors, patients treated at rural hospitals had 27% lower odds of receiving colonoscopy relative to patients treated at urban hospitals (OR = 0.73, $P < 0.0001$) (Table 2). There were several other factors associated with receiving a colonoscopy. For example, women had 4.4% lower odds of receiving colonoscopy (OR = 0.96, $P < 0.0001$), and non-white patients were more likely to receive a colonoscopy. Patients with more comorbidities were less likely to receive colonoscopy; each additional one-point increase in the Charlson comorbidity index was associated with 5.1% lower odds of colonoscopy. Patients who were receiving care at small (OR = 0.90, $P < 0.0001$) and medium (OR = 0.92) sized hospitals were less likely to receive colonoscopy relative to patients receiving care at large hospitals.

Patients who received colonoscopy had a significantly lower likelihood of in-hospital mortality (Table 3). After controlling for other factors, colonoscopy was associated with a 50% lower odds of mortality (OR = 0.50, $P < 0.0001$). In addition, patients treated at rural hospitals had a 5% greater odds of mortality (OR = 1.05, $P = 0.58$), but this association was not statistically significant after controlling for colonoscopy utilization. Several other factors were associated with more significant in-hospital mortality, including age and comorbidities. Other factors were protective for mortality, including the female sex, which was associated with 17% lower odds of mortality (OR = 0.83, $P < 0.0001$).

Utilization of colonoscopy was associated with a longer length of hospital stay of 0.72 days ($P < 0.0001$) (Table 4). In addition, patients treated at rural hospitals had a shorter stay of 0.37 d ($P < 0.0001$). Colonoscopy was also associated with higher hospital costs. Patients treated at rural hospitals incurred lower costs of $853 ($P < 0.001$) independent of colonoscopy. Patients admitted for lower gastrointestinal bleeding who received colonoscopy incurred an additional $2,199 in costs ($P < 0.0001$) (Table 5).

To control for potential selection bias in patients receiving treatment at rural hospitals, a propensity score matching analysis was used to match 16177 patients treated at rural hospitals with 16177 similar patients treated at urban hospitals. After matching, there were no significant differences in inpatient or hospital characteristics. Results of the propensity score analysis confirmed the multi-variable model. In the overall (unmatched) cohort, 37.9% of patients treated at rural hospitals received a colonoscopy, while 46% of patients treated at urban hospitals received a colonoscopy ($P < 0.0001$). After matching, 44.7% of patients treated at urban hospitals received colonoscopy ($P < 0.0001$), suggesting that the utilization of colonoscopy between urban and rural hospitals is not related to patient characteristics.

Table 1 Characteristics of patients admitted for lower gastrointestinal bleeding, stratified by geography

Variable	Urban (*n* = 141571)	Rural (*n* = 16177)	*P* value
Age	73.01	74.35	< 0.0001
18-64	24.2%	20.3%	
65-74	22.2%	22.3%	
75-84	27.6%	29.6%	
85+	22.9%	24.5%	
Sex			< 0.0001
Male	48.1%	46.3%	
Female	51.9%	53.7%	
Race			< 0.0001
White	63.9%	74.6%	
Black	18.5%	10.8%	
Hispanic	8.2%	2.3%	
Asian	2.7%	1.9%	
Other	2.1%	1.0%	
Missing	4.6%	9.4%	
Payer			< 0.0001
Medicare	74.3%	78.8%	
Medicaid	5.4%	4.3%	
Commercial	16.0%	12.4%	
Other	4.3%	4.4%	
Missing	0.1%	0.3%	
Comorbidities			
Number	1.38	1.32	< 0.0001
Charlson index	1.89	1.77	< 0.0001
Colonoscopy			< 0.0001
Yes	45.1%	37.9%	
No	54.9%	62.1%	
Hospital bed size			< 0.0001
Small	15.5%	10.8%	
Medium	29.5%	18.9%	
Large	54.9%	70.2%	
Region			< 0.0001
Northeast	33.2%	21.8%	
Midwest	44.2%	20.8%	
South	50.0%	39.9%	
West	28.4%	17.4%	
Teaching			< 0.0001
No	45.5%	100.0%	
Yes	54.5%	0.0%	

DISCUSSION

Patients who present with gastrointestinal bleeds should undergo a thorough history, physical examination, lab work, and diagnostic procedure to determine the source of bleeding (upper GI tract, colon, or small bowel) and identify the pathology of the bleed. Colonoscopy is the most popular procedure for diagnosing, risk stratifying, and treating colonic bleeding[16]. It is often challenging to manage lower GI bleeding because of the wide variety of pathology that can lead to a lower gastrointestinal bleed. With advancements in endoscopic technology it is modality of choice for lower gastrointestinal bleeds as it allows for diagnosis and treatment simultaneously[17]. Approximately 15% of patients with presumed LGIB are ultimately found to have an upper GI source for their bleeding, highlighting the importance of receiving a timely colonoscopy[18].

Our study demonstrates that patients with LGIB admitted to rural hospitals are less likely to receive colonoscopy for the diagnosis and management, with an odds ratio of 0.73 (95%CI: 0.71-0.76, $P < 0.0001$). Results also showed that the disparity gap has narrowed over the past few years, but we should continue to improve availability of colonoscopy in rural hospitals.

Colonoscopy utilization in rural *vs.* urban LGIB patients could be due to several factors. One of the major factors is the lack of specialists, such as gastroenterologists, in rural hospitals. For this reason, colonoscopies in hospitals that are short on subspecialists are often performed by family medicine physicians that are trained in the procedure. Despite the lower rate of colonoscopies, the safety and quality of family physicians performing colonoscopies are highly comparable to specialists performing the same procedure[19]. These findings suggest that increasing the training opportunities for family physicians in performing colonoscopies could potentially alleviate the scarcity of subspecialists in rural hospitals. Rural provider distribution and scarcity challenges have persisted despite significant attempts by federal and state governments to address them over the last three decades[9].

Lack of insurance and the barrier of financial hardship in rural populations may also partly explain the lower rate of colonoscopies performed in rural hospitals. The disproportion of colonoscopies performed in rural *vs* urban hospitals does however show a downward trend after implementing the Affordable Care Act (ACA)[20]. Insufficient public transportation and increased distance and time to travel to urban hospitals to get colonoscopy and specialist health care can also explain the lower rates of colonoscopy utilization in rural patients. Access to primary care is one of the most significant determinants of up-to-date screening status. However, cost barriers and other factors such as poor broadband internet services limit rural residents' access to finding a primary provider[21].

According to the United States census bureau, in 2017, rural counties continued to have higher uninsured residents than urban areas. In entirely rural counties, 12.3% of the population lacked health insurance, compared to 11.3 percent in primarily rural counties (more than half of the people in rural areas) and 10.1 percent in most urban counties (less than half of the population in rural areas)[22]. According to the Medical Expenditure Panel Survey (MEPS), in 2014-2015, 37.0% of rural people and 33.6% of urban people aged 65 years and older were covered by medicare[23].

In a cross-sectional analysis of Center for Disease Control (CDC) data by Cole *et al*[24], rural residents had lower colorectal cancer screening rates (48%; 95%CI: 48%-49%) than urban residents (54%; 95 %CI: 53%- 55%) from 1998 to 2005 after accounting for demographic and health factors. However, the total number of colonoscopy or flexible sigmoidoscopy screenings increased in urban and rural populations from 1998 to 2005[24]. The rural disparity is also shown in a systematic review by Castellanos *et al*[21], who examined studies of patients suffering from cardiovascular diseases between 1990 and 2017. Most published clinical trials showed that patients from rural communities had significantly lower cardiac rehabilitation referral and participation rates than the general population[21].

Our study also showed that older people aged 85 years and above with LGIB were less likely to receive a colonoscopy, perhaps because current guidelines do not recommend routine screening after 75 years. Women with LGIB are less likely to receive a colonoscopy, most likely because lower GI bleeding is more common in men than in women, and men are more likely to undergo colonoscopy[25]. A study by Devani *et al*[26] showed that women were more likely to delay colonoscopy than males, and women were more likely to ignore bleeding than men (Table 2).

The odds of mortality were reduced in all patients who received a colonoscopy, irrespective of rural or urban location, and the mortality was not significantly different in rural and urban hospitals for patients who received a colonoscopy. This supports our observation that colonoscopy utilization is associated with decreased mortality in all patients, and thus it should be offered to all LGIB patients. As shown in our study, there is, however, a statistically significant difference in colonoscopy utilization between rural and urban hospitals. Thus, by increasing colonoscopy availability in rural hospitals, we anticipate a reduction in mortality in rural hospitals. In general, rural populations in the United States are, on average, older and sicker than their urban counterparts[27]. Our study demonstrates that patients with lower gastrointestinal bleeds who underwent colonoscopy had significantly lower mortality than those with LGIB who did not undergo colonoscopy. This effect was observed after controlling for meaningful patient and hospital characteristics (Table 3). This highlights the significant impact colonoscopy can play in patients with LGIB.

Table 2 Results of multivariable model of colonoscopy utilization

Variable	OR	95%CI		*P* value
		Lower	Upper	
Rural	0.730	0.705	0.757	< 0.0001
Age				
18-64	Reference			
65-74	0.978	0.946	1.010	0.177
75-84	0.986	0.954	1.018	0.384
85+	0.826	0.798	0.855	< 0.0001
Sex				
Male	Reference			
Female	0.956	0.937	0.976	< 0.0001
Race				
White	Reference			
Black	1.224	1.191	1.258	< 0.0001
Hispanic	1.206	1.160	1.253	< 0.0001
Asian	1.222	1.148	1.301	< 0.0001
Other	1.158	1.078	1.244	< 0.0001
Missing	1.107	1.057	1.159	< 0.0001
Payer				
Medicare	Reference			
Medicaid	0.986	0.938	1.037	0.590
Commercial	1.068	1.034	1.103	< 0.0001
Other	1.076	1.020	1.135	0.007
Missing	0.763	0.579	1.004	0.053
Hospital bed size				
Small	0.899	0.873	0.925	< 0.0001
Medium	0.919	0.898	0.940	< 0.0001
Large	Reference			
Teaching				
No	Reference			
Yes	0.951	0.931	0.972	< 0.0001
Charlson comorbidity index	0.949	0.944	0.955	< 0.0001

Patients aged 85 years and above with LGIB had higher mortality rates than patients aged 18-64 years. This may partly be explained by the fact that current guidelines do not recommend routine screening after the age of 75 years, and also, they have confounding prognostic factors compared to younger patients (Table 3). Other research has shown that independent predictors of in-hospital mortality include age, intestinal ischemia, comorbid illness, bleeding while hospitalized for a separate process, coagulation defects, hypovolemia, transfusion of packed red blood cells, and male gender[4].

Women with LGIB had lower mortality rates than men regardless of the treatment setting. These results were comparative to a retrospective observational study by Devani *et al*[26], who found that the odds of mortality were almost 17% lower in women with LGIB than in men.

Our study showed that patients with LGIB admitted to rural hospitals had 8 to 9 h (0.37 d) shorter length of hospital stay than patients admitted to urban hospitals. This can be due to the likelihood that rural populations were less likely to undergo colonoscopy, which extends admissions, as rural hospitals have fewer resources and specialists to perform colonoscopies. Rural populations may also get discharged earlier due to poor insurance benefits and higher inpatient admission costs. Most rural

Table 3 Multivariable model of mortality

Variable	OR	95%CI		*P* value
		Lower	Upper	
Rural	1.050	0.888	1.242	0.567
Colonoscopy				
Yes	0.498	0.446	0.557	< 0.0001
No	Reference			
Age				
18-64	Reference			
65-74	0.939	0.780	1.130	0.504
75-84	1.333	1.121	1.584	0.001
85+	2.132	1.797	2.530	< 0.0001
Sex				
Male	Reference			
Female	0.828	0.749	0.915	< 0.0001
Race				
White	Reference			
Black	0.961	0.835	1.106	0.579
Hispanic	0.694	0.556	0.867	0.001
Asian	1.063	0.784	1.443	0.693
Other	0.960	0.665	1.385	0.826
Missing	0.944	0.750	1.187	0.621
Payer				
Medicare	Reference			
Medicaid	0.941	0.718	1.235	0.662
Commercial	0.834	0.695	1.002	0.052
Other	0.774	0.556	1.077	0.129
Missing	0.538	0.074	3.905	0.540
Hospital bed size				
Small	0.911	0.786	1.057	0.218
Medium	0.966	0.862	1.083	0.552
Large	Reference			
Teaching				
No	Reference			
Yes	0.987	0.887	1.099	0.813
Charlson comorbidity index	1.239	1.215	1.263	< 0.0001

patients (37.01% of patients aged 65 years and older) have Medicare insurance[25] that has a prospective payment system, which pays a predetermined, fixed reimbursement to the hospital for a diagnosis irrespective of the length of stay. This payment system might prompt an earlier discharge for rural patients[28].

Patients with LGIB undergoing colonoscopy had a longer length of hospital stay by 17 h (0.72 d) than those who did not (Table 4). The length of time it takes to perform a colonoscopy is determined by the patients' and endoscopists' characteristics. Even though not all colonoscopies are the same, there is no distinction in the time permitted for each colonoscopy when arranging the procedure in the endoscopy suite. As a result, patient wait times vary, impacting the overall length of stay. Factors determining the length of stay (LOS) include overall time spent preparing for an operation, procedure time, insurance

Table 4 Multivariable model of length of hospital stay

Variable	Coefficient	95%CI		*P* value
		Lower	Upper	
Rural	-0.372	-0.444	-0.300	< 0.0001
Colonoscopy				
Yes	0.718	0.677	0.759	< 0.0001
No	Reference			
Age				
18-64	Reference			
65-74	0.133	0.066	0.201	< 0.0001
75-84	0.382	0.315	0.449	< 0.0001
85+	0.518	0.448	0.588	< 0.0001
Sex				
Male	Reference			
Female	0.067	0.026	0.109	0.001
Race				
White	Reference			
Black	0.590	0.534	0.646	< 0.0001
Hispanic	0.016	-0.064	0.095	0.699
Asian	-0.041	-0.169	0.088	0.534
Other	0.091	-0.057	0.238	0.227
Missing	-0.183	-0.277	-0.089	< 0.0001
Payer				
Medicare	Reference			
Medicaid	-0.047	-0.150	0.055	0.367
Commercial	-0.386	-0.453	-0.319	< 0.0001
Other	-0.403	-0.513	-0.292	< 0.0001
Missing	-0.079	-0.631	0.473	0.779
Hospital bed size				
Small	-0.451	-0.511	-0.391	< 0.0001
Medium	-0.235	-0.283	-0.188	< 0.0001
Large	Reference			
Teaching				
No	Reference			
Yes	0.297	0.253	0.341	< 0.0001
Charlson comorbidity index	0.232	0.221	0.243	< 0.0001
Intercept	3.173	3.097	3.249	< 0.0001

reimbursement, and out-of-pocket expenses, influencing hospital and patient decision-making[29].

Our study showed that rural patients with LGIB incur $853 less in costs than patients treated at urban hospitals which could be due to the fact that rural patients are less likely to undergo colonoscopy, which can be contributory to the reduction of the total inpatient admission cost.

Our study showed that patients with LGIB who undergo colonoscopy incur $2199 in higher costs than those who do not. Procedural costs and longer duration of stay for patients undergoing colonoscopy may be part of the higher costs. A cost-effectiveness analysis study comparing four diagnostic strategies in the evaluation of rectal bleeding in adults by Allen *et al*[30] using a Markov

Table 5 Multivariable model of inpatient admission costs

Variable	Coefficient	95%CI		*P* value
		Lower	Upper	
Rural	-$853.03	-$1059.62	-$646.44	< 0.0001
Colonoscopy				
Yes	$2198.68	$2080.08	$2317.27	< 0.0001
No	Reference			
Age				
18-64	Reference			
65-74	$353.75	$159.71	$547.79	< 0.0001
75-84	$569.47	$377.06	$761.87	< 0.0001
85+	$184.80	-$16.82	$386.42	0.072
Sex				
Male	Reference			
Female	-$487.40	-$606.30	-$368.49	< 0.0001
Race				
White	Reference			
Black	$1065.28	$903.76	$1226.81	< 0.0001
Hispanic	$571.60	$343.11	$800.10	< 0.0001
Asian	$2228.13	$1858.86	$2597.39	< 0.0001
Other	$938.42	$514.93	$1361.92	< 0.0001
Missing	-$223.19	-$492.88	$46.49	0.105
Payer				
Medicare	Reference			
Medicaid	$209.94	-$85.38	$505.27	0.164
Commercial	-$432.66	-$624.55	-$240.77	< 0.0001
Other	-$788.60	-$1105.57	-$471.62	< 0.0001
Missing	-1065.893	-2652.626	520.839	0.188
Hospital bed size				
Small	-$418.08	-$590.47	-$245.70	< 0.0001
Medium	-$305.15	-$440.76	-$169.54	< 0.0001
Large	Reference			
Teaching				
No	Reference			
Yes	$604.62	$477.91	$731.33	< 0.0001
Charlson comorbidity index	$601.63	$570.19	$633.06	< 0.0001
Intercept	$7859.86	$7642.30	$8077.41	< 0.0001

model showed that in addition to being associated with lower mortality, colonoscopy was also cost-effective when compared to flexible sigmoidoscopy, flexible sigmoidoscopy followed by air contrast barium enema (FS+ACBE), and simple observation. Additional research is needed to understand the value proposition of colonoscopy for LGIB other than rectal bleeding. This is perhaps because patients undergoing colonoscopy are more likely to stay longer in the hospital and spend higher costs than those who do not undergo colonoscopy. Increases in LOS per day were linked to a 47% increase in Inpatient admission costs[26]. The total cost of a colonoscopy depends on whether costs are assessed from a societal or a health system perspective[31].

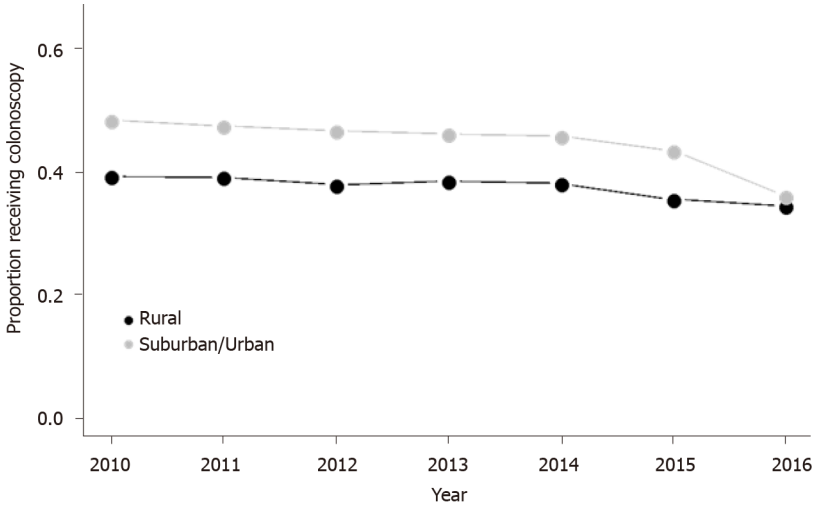

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Figure 1 Trends in utilization of colonoscopy for patients admitted for lower gastrointestinal bleeding.

One strength of the study is that we used data from NIS, HCUP, provided by the AHRQ. This is a nationally representative sample, which enhances the generalizability of our findings.

Limitations of the study

We could not account for the severity of LGIB or the screening status of patients. Also, we studied admissions between 2010 and 2016 which is the most recent database and there is not currently more recent data. A limitation is that the NIS data set is based solely on ICD-9 and ICD-10 diagnoses. Specific colonoscopy findings are not reported in the NIS data set.

CONCLUSION

Our study results demonstrated that the rate of utilization of colonoscopy was significantly lower in rural hospitals compared to urban hospitals. This study also showed that patients with lower gastrointestinal bleeds undergoing colonoscopy had significantly lower in-hospital mortality than those who did not. The study results emphasize the importance of counseling rural patients and educating them about the life-threatening complications of LGIB, which colonoscopy can avoid. Furthermore we would benefit from more access to colonoscopies in rural settings. Internal medicine and family physicians should be trained to perform colonoscopies in rural settings to increase the availability of colonoscopy in these areas. Physicians should be encouraged to improve rural population outreach, hospital resources, and reimbursement. Despite differences in colonoscopy utilization, this study did not show any significant difference in mortality between rural and urban patients with LGIB. Further studies are needed to give more insights into rural-urban disparities in mortality.

ARTICLE HIGHLIGHTS

Research background

Disparities in colonoscopy access in rural and urban hospitals is an understudied topic. The significance of this study is to demonstrate whether or not improved access improves patient mortality.

Research motivation

To improve access to colonoscopies in the United States. We are also interested in the availability of colonoscopy and how it effects patients length of stay and costs.

Research objectives

To discover whether or not there is a disparity in colonoscopy utilization for lower gastrointestinal bleeds between rural and urban hospital areas in the United States. Also to determine whether there is a benefit for mortality in patients with lower gastrointestinal bleeds when they receive colonoscopies.

Research methods

Retrospective cohort study and data analysis of National Inpatient Sample, Healthcare Cost and Utilization Project, provided by the Agency for Healthcare Research and Quality.

Research results

Approximately 37.9% of patients with lower gastrointestinal bleeding received colonoscopy at rural hospitals compared to 45.1% at urban hospitals. Patients treated at rural hospitals had 27% lower odds of receiving colonoscopy relative to patients treated at urban hospitals (OR = 0.73, $P < 0.0001$) After controlling for other factors, colonoscopy was associated with a 50% lower odds of mortality (OR = 0.50, $P < 0.0001$). The problem that remains to be solved is providing patients in rural hospitals access to colonoscopy so more patients can have a mortality benefit when they present with a lower gastrointestinal bleed.

Research conclusions

This study proposes that because there is a decrease in mortality when patients receive a colonoscopy, we should improve access to colonoscopies in rural hospitals. New methods proposed are increased access to specialists and increased training opportunities for primary care providers for colonoscopies.

Research perspectives

Future research should be aimed at determining mortality differences in patients with lower gastrointestinal bleeds that receive colonoscopy between urban and rural hospitals.

FOOTNOTES

Author contributions: Ganta N and Aknouk M contributed equally to this work; Ganta N, Aknouk M, Nikiforov I, Bommu VJL, Patel V, Cheriyath P, Hollenbeak C, and Hamza A, designed the research study; Ganta N, Aknouk M, Alnabwani D, Nikiforov I, Bommu VJL, Patel V, and Hollenbeak C performed the research; Hollenbeak C, Nikiforov I, and Cheriyath P contributed in statistical analysis; Ganta N, Aknouk M, Alnabwani D, Nikiforov I, Bommu VJL, Patel V, and Hollenbeak C analyzed the data and wrote the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Percutaneous transluminal angioplasty balloons for endoscopic ultrasound-guided pancreatic duct interventions

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Abstract

BACKGROUND

Endoscopic ultrasound (EUS)-guided main pancreatic duct (PD) access may be used when conventional endoscopic retrograde cholangiopancreatography (ERCP) techniques fail. The use of a percutaneous transluminal angioplasty balloon (PTAB), originally developed for vascular interventions, can be used to facilitate transmural (*e.g.*, transgastric) PD access and to dilate high-grade pancreatic strictures.

AIM

To describe the technique, efficacy, and safety of PTABs for EUS-guided PD interventions.

METHODS

Patients who underwent EUS with use of a PTAB from March 2011 to August 2021 were retrospectively identified from a tertiary care medical center supply database. PTABs included 3-4 French angioplasty catheters with 3-4 mm balloons designed to use over a 0.018-inch guidewire. The primary outcome was technical success. Secondary outcomes included incidence of adverse events (AEs) and need for early reintervention.

RESULTS

A total of 23 patients were identified (48% female, mean age 55.8 years). Chronic pancreatitis was the underlying etiology in 13 (56.5%) patients, surgically altered anatomy (SAA) with stricture in 7 (30.4%), and SAA with post-operative leak in 3 (13.0%). Technical success was achieved in 20 (87%) cases. Overall AE rate was 26% (n = 6). All AEs were mild and included 1 pancreatic duct leak, 2 cases of post-procedure pancreatitis, and 3 admissions for post-procedural pain. No

patients required early re-intervention.

CONCLUSION

EUS-guided use of PTABs for PD access and/or stricture management is feasible with an acceptable safety profile and can be considered in patients when conventional ERCP cannulation fails.

Key Words: Dilating balloon; Pancreatic duct intervention; Chronic pancreatitis; Anastomotic stricture

Core Tip: Endoscopic ultrasound (EUS)-guided access of the main pancreatic duct (MPD) can be used to perform endotherapy when conventional endoscopic retrograde cholangiopancreatography fails. After access to the MPD is obtained, the tract created between the gastrointestinal lumen and pancreatic duct must be dilated prior to any further intervention. Percutaneous transluminal angioplasty balloons, originally developed for vascular interventions, can be used to access the pancreatic duct effectively and safely, as well as dilate high-grade MPD strictures if needed. Interventional endoscopists should be familiar with these cross-platform balloons as additional tools in the toolbox for EUS-guided MPD endotherapy.

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INTRODUCTION

Obstruction of the main pancreatic duct (MPD) can occur in the context of chronic inflammation and fibrosis due to a variety of clinicopathologic conditions, including both malignant and benign etiologies (*e.g.*, chronic pancreatitis, post-pancreatic surgery). Obstruction of MPD outflow leads to higher resistance to pancreatic secretions, intraductal hypertension, and ultimately ductal dilation[1,2]. Patients can present with chronic abdominal pain, recurrent pancreatitis, steatorrhea, and unexplained weight loss. Decompression of the PD is the mainstay of treatment for symptomatic patients, and endoscopic therapy has become the preferred treatment modality due to its safety profile when compared to surgery[3,4].

Transpapillary or transanastomotic drainage with endoscopic retrograde cholangiopancreatography (ERCP) remains the preferred approach for endoscopic pancreatic duct access and intervention[5]. While successful in the vast majority of cases, 3% to 10% fail due to inability to cannulate the papilla/anastomosis, obstructive stones, high-grade strictures, and surgically-altered anatomy (SAA) that impacts access to the pancreaticobiliary tree, including surgeries like Roux-en-Y gastric bypass and pancreaticoduodenoctomy[6]. In these cases, endoscopic ultrasound (EUS)-guided pancreatic duct drainage has emerged as a potential salvage approach with a favorable safety profile and technical success rate. Technical and clinical success rates range from 63% to 100% and 76% to 100%, respectively, with adverse event rates ranging from as low as 14% up to 37%[7]. Guidelines recommend consideration of EUS-guided access in multidisciplinary, tertiary care settings when conventional therapy fails [8].

As EUS-guided pancreatic duct access becomes more established among experienced operators, there remains significant variation in technique. Specifically, dilation of the access tract can be performed with a variety of devices and currently published studies include the utilization of hydrostatic balloons, tapered catheters, and electrocautery-enhanced catheters[9,10]. No comparative trials exist comparing the success and complication rates of these devices. The hydrostatic balloons which are currently used were designed for biliary intervention, and their size may increase the risk of complications during pancreatic duct access[11].

Percutaneous transluminal angioplasty balloons (PTAB) are smaller caliber, 3 to 4mm diameter balloons initially designed for vascular interventions but can passed over standard 0.018-inch guidewires for use on endoscopic platforms. Initial case reports described the use of these balloons to treat otherwise impassable biliary strictures[12]. Their size makes them well-suited for dilation of the pancreaticogastrostomy/enterostomy as well as high-grade MPD strictures. Reports describe the use of these devices during ERCP; however, experience during EUS is limited to a handful of reported cases

[13,14]. The objective of this study is to describe the use of PTABs during EUS-guided MPD interventions. This includes the technique, efficacy, and safety of their use during these procedures.

MATERIALS AND METHODS

Study overview

This is a retrospective, single-center cohort study approved by the Institutional Review Board at the Mayo Clinic. Consecutive patients who underwent EUS-guided MPD intervention with use of a PTAB between March 2011 to August 2021 were identified from a single tertiary care center using a supply database. Balloons used included 3 and 4 mm diameter SAVVY™ and SABER™ PTA balloons (Cordis, Santa Clara, CA, United States) which were 20 mm in length. Procedure information was extracted *via* manual chart review and included procedure indication, inpatient status, preceding ERCP attempts, indication for EUS-guided approach, maximum diameter of the MPD measured intraprocedurally, site of MPD access, and location of balloon dilation (Figure 1). In patients with SAA, the exact procedure was recorded. Patients with post-surgical pancreatic leaks were classified as biochemical leaks, grade B, or grade C according to the International Study Group for Pancreatic Fistula criteria[15].

The primary outcome was technical success defined by successful MPD access and accomplishing the intent of the procedure. If either of these conditions were not met, the procedure was classified as technical failure. Secondary outcomes included procedural related adverse events (AEs) including pain, bleeding, pancreatitis, leak, new fluid collection, perforation, or death as well as need for early reintervention prior to planned follow-up and clinical success. AEs were classified as mild, moderate, or severe based on American Society of Gastrointestinal Endoscopy (ASGE) lexicon[16]. Clinical response was noted at last follow up. Complete response was noted when there was clear documentation that all clinical symptoms fully resolved after intervention, and partial response if it any improvement in severity or frequency was documented. Patients without any benefit were classified as persistent symptoms.

Procedural technique

All procedures were performed by EUS- and ERCP-trained interventional endoscopists in a dedicated endoscopy unit with patients under general anesthesia. Due to the retrospective nature of this study, the exact technique used in each case was operator dependent. Generally, a linear-array echoendoscope was passed into the stomach and the MPD was identified. The MPD was preferentially accessed through the gastric wall with an FNA needle (19- to 22-gauge); however, the small bowel was also evaluated as an access point if suitable endosonographic windows for duct puncture were not found in the stomach. After EUS-guided ductal access was achieved, an 0.018-inch guidewire was passed under fluoroscopic guidance into the MPD and through the ampulla/anastomosis when possible. When utilized, the PTAB was then advanced over the guidewire and used to dilate the access tract and/or pancreatic duct stricture prior to any additional intervention, including further dilation or stenting (Figure 2).

Statistical analysis

Data management, analysis, and visualization was performed using BlueSky Statistics software (version 7.10, BlueSky Statistics LLC, Chicago, IL, United States). Quantitative variables were described with median value and interquartile range (IQR). Categorical data were reported as relative proportions (%).

RESULTS

Patient characteristics

A total of 23 patients were identified. The median age of the cohort was 55.8 years (IQR 45.0-57.8) with 11 (48%) females and 12 (52%) males. Median body mass index was 25.8 kg/m^2 (IQR 23.9-27.5). Procedural indications included chronic pancreatitis in 13 (57%) patients, SAA with stricture in 7 (30%), and SAA with post-operative leak in 3 (13.0%). Of the 10 patients with SAA, 9 had undergone pancreaticoduodenectomy with antrectomy (*i.e.*, Whipple procedure) and 1 had an en-bloc resection of metastatic cervical cancer requiring hepaticogastrostomy with Roux-en-Y reconstruction. The 3 post-operative leaks were identified as nonspecific peripancreatic fluid on computed tomography and confirmed by ERCP. All cases were classified as grade B and none were associated with organ failure or need for operative reintervention. Indications for an EUS-guided approach included 5 cases with inaccessible anastomosis/ampulla (22%), 5 obstructive anastomotic strictures (22%), 2 failed cannulations (9%), 9 proximal obstructions due to stone or stricture (9, 39%), and 2 disconnected pancreatic ducts (9%).

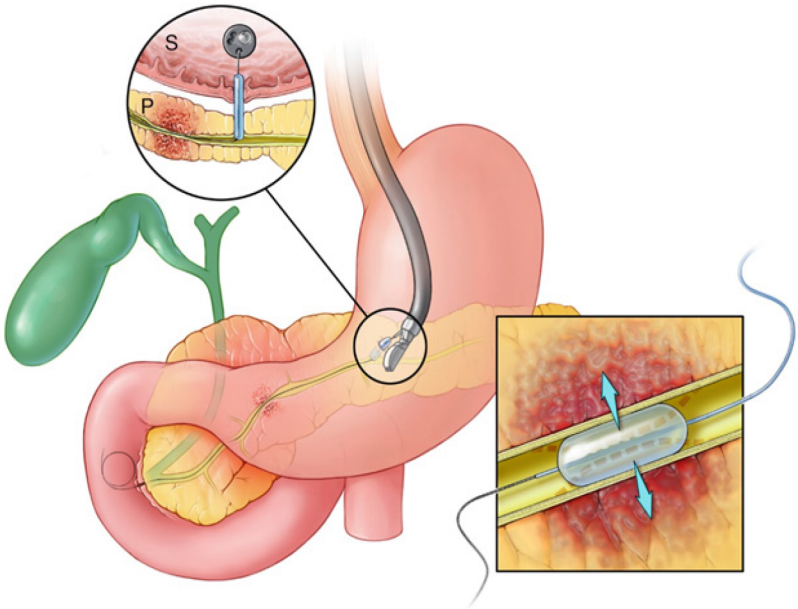

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Figure 1 Illustration of endoscopic ultrasound-guided pancreatic duct access showing balloon dilation of the gastropancreatic fistula.
The balloon can also be passed into the main pancreatic duct to dilate high grade strictures.

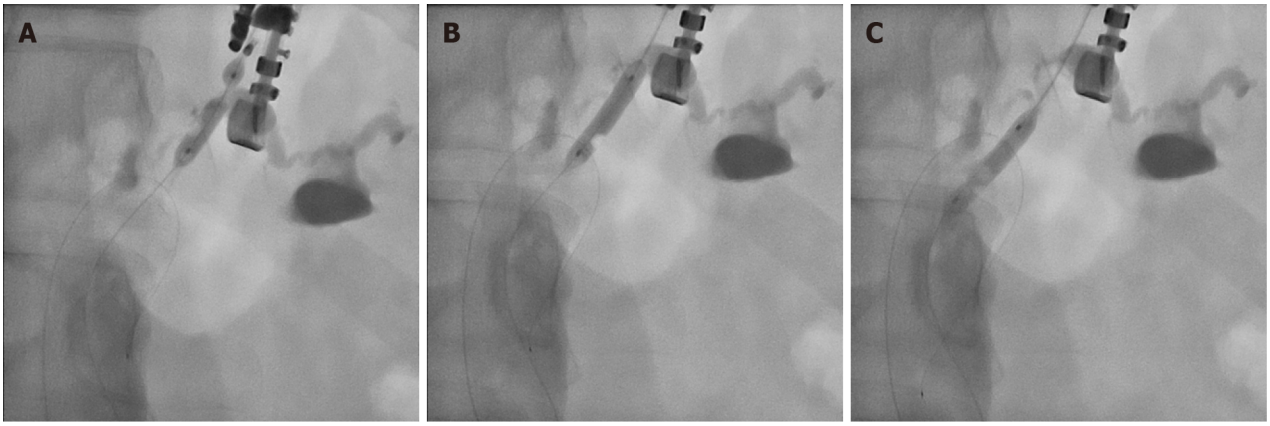

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Figure 2 Fluoroscopy images taken during endoscopic ultrasound showing dilation of access tract and stricture in a patient with chronic pancreatitis and a disconnected duct (A-C).

Procedural details

The majority of procedures were performed as an outpatient (n = 18, 78%). Maximum MPD size as measured during EUS was 5.5 mm (IQR 3.7-8.3 mm). Transgastric access was obtained in 22 cases (96%) with 1 pancreaticoenterostomy performed (4%). A 4 mm diameter PTAB was used in 15 cases (65%) with 3 mm balloons used in the remaining 8 (35%). The pancreatic duct was typically accessed through the body (n = 17, 74%) followed by tail (n = 3, 13%), and head (n = 3, 13%). The balloons were primarily used to dilate the access tract in 21 cases (91.3%), of which 9 were then passed into the pancreas and used for PD dilation. Pancreatic duct dilation alone was performed in 2 cases (10%). Dilation with a PTAB was the initial method used in the majority of cases (n = 21, 91%). In the remaining 2 cases, PTAB was used if needle knife access puncture and a dilating catheter was not successful. Further pancreatic duct intervention with dilation was performed in 5 cases (22%) and stenting in 17 (74%). This included 9 transmural stents terminating in the MPD, 8 stents placed through the stomach which traversed the MPD into the small bowel, and 1 retrograde transpapillary stent terminating in the MPD.

Outcomes

Technical success was achieved in 20 cases (87%). All 3 failed cases occurred in patients with chronic, calcific pancreatitis. In 2 of these cases, the procedure failed due to inability to obtain an adequate

window for MPD access. The third case failed due to a high-grade MPD stricture with calcified stones that prevented the passage of all devices, including the 4 mm PTAB.

AEs were noted in 6 patients (26%) which were all mild in severity, requiring an unplanned hospital admission for ≤ 3 nights. Additional patient and procedural factors that may have impacted AEs are outlined in Table 1. There was 1 case of pancreatic duct leak identified endosonographically during the procedure, which was self-contained and managed conservatively. Additionally, there were two cases of pancreatitis and 3 cases of post-procedural pain requiring hospital admission. There were no AEs related to bleeding from the access site or perforation.

Median post-procedure follow up time was 13.9 mo (IQR 6.9-28.1 mo). No patients required unanticipated, early intervention. In the 20 cases that were technically successful, 14 underwent additional planned interventions prior to stent removal which included routine stent exchange in 7 cases and placement of a parallel stent in the remaining 7. At the time of last follow up, 9 of the 20 (45.0%) technically successful cases were noted to have complete resolution of symptoms, 5 (25.0%) partial resolution, and 3 (15%) persistent symptoms. One patient (4.3%) did not have follow up symptoms documented, and two (8.6%) died during follow up prior to assessment of symptom improvement.

DISCUSSION

The emergence of interventional EUS has given endoscopists the ability to treat pancreatic duct obstruction even when conventional ERCP fails. These interventions require dilation of the gastro- or enteropancreatic fistula created during EUS-guided pancreatic duct drainage. Given the lack of dedicated devices to facilitate EUS-directed drainage interventions, endoscopists rely on other accessories that were not designed for these interventions. These include hydrostatic pancreaticobiliary dilating balloons, tapered dilating catheters, traction sphincterotome, and diathermy-compatible catheters[13]. PTABs are yet another device that can be used to facilitate access with interventional EUS.

Each technique and device carries its own risk-benefit profile. Axial pressure forces created during dilation with a fixed-diameter catheter, cannula or tapered passage dilator can lead to dissection of the tissue planes. On the other hand, balloon dilation may increase the risk of perforation, leakage, and bleeding due to its "all-or-nothing" approach. Standard endoscopic balloon dilators typically have diameters of 5 to 6 French and were designed primarily for intraductal ERCP-guided interventions. The use of smaller diameter balloons theoretically may allow for controlled dilation of the tract while minimizing the risk of perforation and leak. Notably, all AEs in this cohort were mild, without significant bleeding or perforation. There was one, self-contained pancreatic duct leak, but this occurred in a case where a diathermy catheter was used prior to balloon dilation. Electrocautery devices can result in a delayed-burn effect, increasing the risk of developing serious adverse events[17]. The overall AE rate of 26% may seem high compared to other standard endoscopic procedures but is favorable when compared to the morbidity and mortality associated with surgical alternatives, which include AE rates of up to 30% and 2% mortality[18,19]. Our data is similar to published literature on EUS-guided drainage of the MPD with more conventional ERCP accessories, including one of the largest multicenter studies which reported an AE rate of 20%[12].

Technical success of EUS-guided drainage of the MPD ranges from 50%-100% in the literature, approaching 80%-90% in more recent cohorts with experienced operators[10,12]. A technical success rate of 87% is consistent with the higher end of this range. In a previously published case series on the utilization of PTABs during EUS-guided interventions, a very similar technical success rate of 88% was reported with only one mild adverse event[15]. However, this was a very small cohort of 8 patients, contained only 1 case of chronic pancreatitis with stricture, and details regarding other procedural factors that may have impacted outcomes were limited. In this study, we report on a robust cohort with chronic pancreatitis and post-surgical disease. The majority of PTABs were successfully used as first line EUS-guided therapy, as opposed to salvage therapy when other devices failed. Furthermore, two of the three failures were due to limited mobility and inability to secure a safe window for MPD access, which is a limitation of the procedure itself and not the dilation device used.

This study is limited by its retrospective design with slight variations in patient characteristics and procedural technique. However, this heterogeneity also highlights that PTABs can be used in a wide range of clinical scenarios. Furthermore, procedural outcomes were certainly confounded by patient and technical factors unrelated to PTAB use. This study was not designed to evaluate EUS-guided drainage of the MPD outcomes overall, and additional detail was provided regarding cases of technical failure and AEs to allow for careful evaluation of the role the device played in these outcomes.

CONCLUSION

This study suggests that PTABs can be used to successfully and consistently access and drain the pancreatic duct while maintaining a high technical success rate without severe AEs. Additional comparative studies are needed to determine optimal technique; however, these cross-platform devices

Table 1 Procedural adverse event details

	Adverse Event	Severity	Additional devices used for tract dilation	Other procedural detail
1	Post-procedure pain	Mild[1]	None	None
2	Post-procedure pain	Mild[1]	None	Multiple puncture attempts; Needle dislodgement requiring retrieval with forceps
3	Post-procedure pain	Mild[1]	None	Dehiscence of surgical anastomosis noted prior to procedure start
4	Pancreatic duct leak	Mild[1]	Needle knife electrocautery	Electrocautery utilized prior to percutaneous angioplasty balloon dilation; Small, self-contained leak identified sonographically prior to completion of the procedure
5	Pancreatitis	Mild[1]	None	Additional pancreatic duct dilation to 6 mm; Large fragmented pancreatic duct stone cleared in an antegrade fashion with occlusion balloon
6	Pancreatitis	Mild[1]	None	Small endoscopic window with limited mobility; Multiple puncture attempts

[1]Post-procedure hospitalization ≤ 3 d.

can help address the safety and technical limitations of existing endoscopic devices including larger diameter balloons, fixed diameter catheters, tapered passage dilators, and electrocautery-based devices. Interventional endoscopists should be familiar with these devices as additional tools in the toolbox for EUS-guided MPD endotherapy.

ARTICLE HIGHLIGHTS

Research background

While endoscopic retrograde cholangiopancreatography (ERCP) remains the gold standard for main pancreatic duct (MPD) intervention, endoscopic ultrasound (EUS)-guided MPD access has emerged as a safe and effective alternative when ERCP fails. A key step in EUS-guided intervention is dilation of the tract created between the gastrointestinal lumen and pancreatic duct, however there is limited data regarding the optimal dilation device and technique. Furthermore, current tools were designed primarily for biliary intervention, including hydrostatic balloons, tapered bougies, and electrocautery-enhanced catheters.

Research motivation

A small diameter, hydrostatic balloon would theoretically allow for safe dilation while minimizing the risk of adverse events, however commercially available devices are limited. Percutaneous angioplasty balloons (PTABs) are small diameter balloons that were initially designed for vascular interventions. They can be deployed over a standard guidewire and utilized on endoscopic platforms to dilate the access tract created during EUS-guided access as well as high grade strictures. However, data on the use of these devices is limited to a handful of case reports.

Research objectives

The main objective of this study is to describe the efficacy and safety of PTAB use during EUS-guided MPD access. The primary outcome was technical success with secondary outcomes of clinical success and adverse event rate. The objectives of this study provide key, real-word information on the use of PTABs for clinicians as well as preliminary data to inform future prospective studies.

Research methods

This is a retrospective, single center cohort study performed at an academic tertiary care center which includes all patients from 2011 to 2021 who underwent EUS-guided MPD which utilized a PTAB. Patients were identified retrospectively from a procedural supply database and clinical information was extracted from the electronic medical record.

Research results

A total of 23 cases were identified. Intervention was performed in the setting of chronic pancreatitis in 13 (56%), post-surgical stricture in 8 (35%), and post-surgical leak in 2 (9%). Technical success was achieved in 20 (87%) cases with 6 (26%) adverse events. Adverse events were all mild in severity and included 3 admissions for post-procedural pain, 2 pancreatitis, and 1 pancreatic duct leak.

Research conclusions

This study demonstrates that PTABs can be used to consistently access the MPD for EUS-guided interventions with an acceptable safety profile. In the absence of dedicated devices, endoscopists can consider using cross-platform PTABs for initial dilation prior to antegrade interventions.

Research perspectives

Further prospective, randomized studies are needed to compare the efficacy and safety of PTABs to other dilating devices and techniques.

FOOTNOTES

Author contributions: AbiMansour JP collected the data, performed the analysis and wrote the paper; Abu Dayyeh BK, Levy MJ, Storm AC, Martin JA, Petersen BT, Law RJ, and Topazian MD performed the procedures, obtained the data, and critically reviewed the manuscript; and Chandrasekhara VC designed the research and provided supervision, manuscript review, and final approval.

Institutional review board statement: This study was reviewed and approved by the Mayo Clinic Institutional Review Board (IRB No. 20-0055740).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: Andrew C Storm is a consultant for Apollo Endosurgery; and received research support from Apollo Endosurgery and Boston Scientific. Ryan J Law is a consultant for ConMed and Medtronic and receives royalties from UpToDate. Bret T Petersen is a consultant for Olympus America and investigator for Boston Scientific and Ambu. Barham K Abu Dayyeh reports consultant roles with Endogenex, Endo-TAGSS, Metamodix, and BFKW; consultant and grant or research support from USGI, Cairn Diagnostics, Aspire Bariatrics, Boston Scientific; speaker roles with Olympus, Johnson and Johnson; speaker and grant or research support from Medtronic, Endogastric solutions; and research support from Apollo Endosurgery and Spatz Medical. Vinay Chandrasekhara is a consultant for Covidien LP, is on the advisory board for Interpace Diagnostics, and is a shareholder in Nevakar, Inc. The remaining authors have no conflicts or funding to disclose.

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ORIGINAL ARTICLE

Observational Study

New application of endocytoscope for histopathological diagnosis of colorectal lesions

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Abstract

BACKGROUND

The endocytoscope with ultra-high magnification (x 520) allows us to observe the cellular structure of the colon epithelium during colonoscopy, known as virtual histopathology. We hypothesized that the endocytoscope could directly observe colorectal histopathological specimens and store them as endocyto-pathological images by the endoscopists without a microscope, potentially saving the burden on histopathologists.

AIM

To assess the feasibility of endocyto-pathological images taken by an endoscopist as adequate materials for histopathological diagnosis.

METHODS

Three gastrointestinal pathologists were invited and asked to diagnose 40 cases of endocyto-pathological images of colorectal specimens. Each case contained seven endocyto-pathological images taken by an endoscopist, consisting of one loupe image, three low-magnification images, and three ultra-high magnification images. The participants chose hyperplastic polyp or low-grade adenoma for 20 cases of endocyto-pathological images (10 hyperplastic polyps, and 10 Low-grade adenomas in conventional histopathology) in study 1 and high-grade adenoma/

shallow invasive cancer or deep invasive cancer for 20 cases [10 tumor in situ/T1a and 10 T1b] in study 2. We investigated the agreement between the histopathological diagnosis using the endocyto-pathological images and conventional histopathological diagnosis.

RESULTS

Agreement between the endocyto-pathological and conventional histopathological diagnosis by the three gastrointestinal pathologists was 100% (95%CI: 94.0%–100%) in studies 1 and 2. The interobserver agreement among the three gastrointestinal pathologists was 100%, and the κ coefficient was 1.00 in both studies.

CONCLUSION

Endocyto-pathological images were adequate and reliable materials for histopathological diagnosis.

Key Words: Cancer; Colon; Endocytoscopy; Histopathology; Specimen

Core Tip: The endocytoscope allows us to observe the histological structure of the colon epithelium, but it is a virtual histopathology. We directly observed pathological specimens by the endocytoscope and evaluated the practical usefulness of endocyto-pathology in this pilot study.

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INTRODUCTION

The endocytoscope, which was launched in early 2018 by Olympus Medical Systems Corporation (Tokyo, Japan), can provide ultra-high magnification (x 520) images in real time during colonoscopy. The endocytoscopy allows us to observe the cellular structure of the colorectal lesions, known as virtual histopathology and has provided high diagnostic performance in estimating their histopathology[1-5]. There is growing evidence that the diagnostic accuracy of endocytoscopy with computer-aided diagnosis (CAD) was greater than that of non-expert and comparable to expert endoscopists[6-12].

Based on the background of the shortage of histopathologists, we have explored a new application of endocytoscope for histopathological diagnosis of colorectal lesions[13]. We hypothesized that the endocytoscope could directly observe colorectal histopathological specimens and store them as endocyto-pathological images by the endoscopists themselves without a microscope. The endocyto-pathological images taken by endoscopists can be stored in the same system as the endoscopic images so that both images can be obtained as needed, making it possible to hold clinicopathological conferences efficiently even in countries with a few pathologists. Furthermore, a combination of endocyto-pathological images and the CAD system may lead to saving the burden of histopathologists in the future.

This pilot study aimed to assess the feasibility of endocyto-pathological images taken by an endoscopist as adequate materials for histopathological diagnosis.

MATERIALS AND METHODS

Endocyto-pathological images

First, each specimen was placed horizontally in a white container filled with water to control the diffuse reflection of the scope light. An endoscopist (FI) took the ultra-magnifying images of the specimens (endocyto-pathological images) with the right hand firmly fixed by touching the edge of the container and holding the tip of the scope using a penhold grip (Figure 1). This method helps bring high-quality endocyto-pathological images into focus. Seven endocyto-pathological images were obtained for each case (one loupe image, three low-magnification images, and three ultra-high magnification images) (Figures 2 and 3).

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Figure 1 How to take the endocyto-pathological images using an endocytoscope: The right hand was firmly fixed by touching the edge of the container, and the tip of the scope was held in the penhold method.

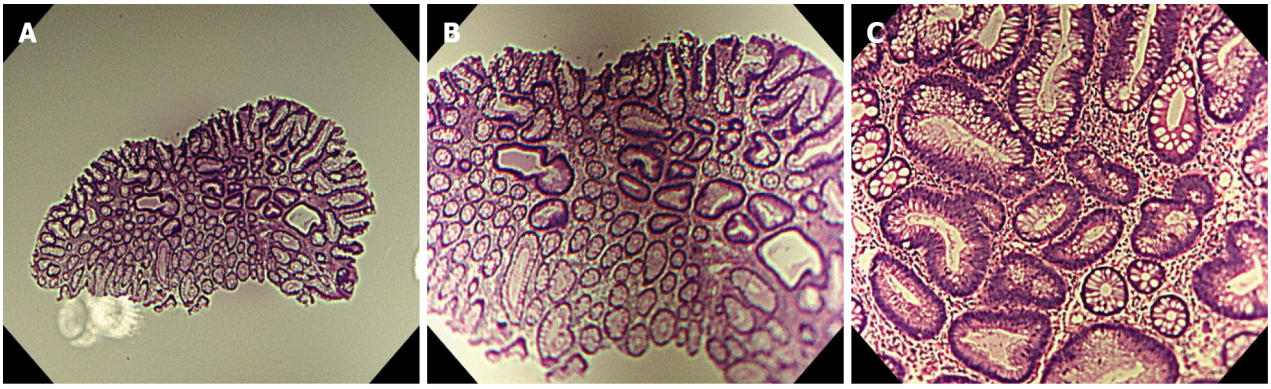

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Figure 2 Endocyto-pathological images of low-grade adenoma. A: Loupe image. B: Low-magnification image. C: Ultra-high magnification image.

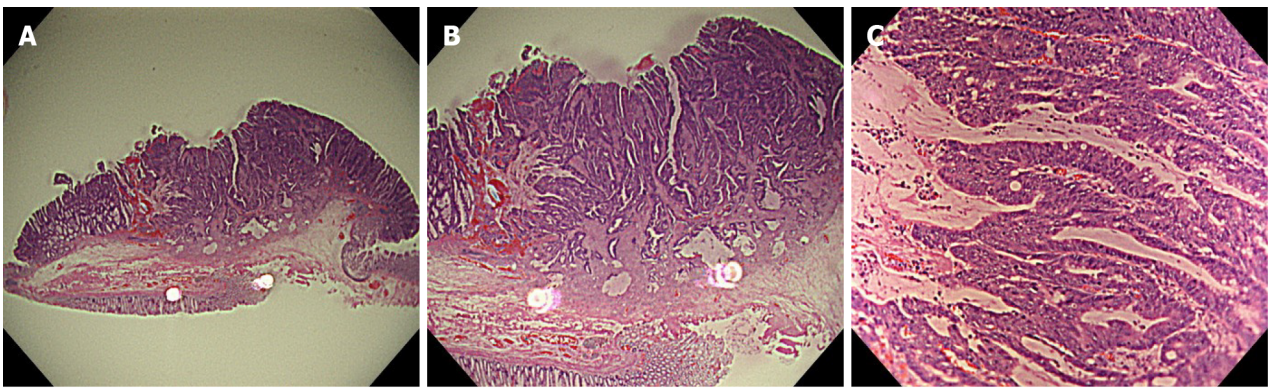

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Figure 3 Endocyto-pathological images of T1b cancer. A: Loupe image. B: Low-magnification image. C: Ultra-high magnification image.

Selection of colorectal specimens

Candidate colorectal specimens were selected from histopathologically-known material obtained by endoscopic or surgical resection at Sano Hospital between January 2017 and January 2021. Candidates samples with poor preservation, incomplete resection of the lesion, or other candidates deemed inappropriate by the investigators were excluded. Among these candidates samples, 10 specimens for each of the following categories hyperplastic polyps, low-grade adenoma, high-grade adenoma/shallow invasive cancer (10 tumor in situ (Tis)/T1a), and deep invasive cancer (T1b) were randomly selected. The number of specimens in each category was masked to the participants.

Evaluation of endocyto-pathological images by gastrointestinal pathologists

Three gastrointestinal pathologists (TS, HK, KI) were invited and asked to read the endocyto-pathological images for 40 cases (7 images for each case) of colorectal specimens from May to July 2021. The participants were asked to choose hyperplastic polyp or low-grade adenoma for 20 cases of endocyto-pathological images (10 hyperplastic polyps and 10 Low-grade adenomas diagnosed by the conventional method) in study 1 and high-grade adenoma/shallow invasive cancer (Tis/T1a) or deep invasive cancer (T1b) for 20 cases (10 Tis/T1a and 10 Tib cancer) in study 2.

The study protocol was reviewed and approved by the Institutional Review Board at Sano Hospital (202106-02). This study was registered with Japan Registry of Clinical Trials (jRCT1050210046).

Outcome measures

The primary outcome measure was the agreement between the histopathological diagnosis using the endocyto-pathological images and conventional histopathological diagnosis.

The secondary outcome measure was the interobserver agreement rate and Fleiss's Kappa statistics among three pathologists.

Statistical analysis

This study was conducted as an exploratory research investigation without calculating sample size due to the lack of data in previous studies.

RESULTS

Tables 1 and 2 show the agreement between the histopathological diagnosis by three gastrointestinal pathologists using the endocyto-pathological images and conventional histopathological diagnosis in differentiating low-grade adenoma from hyperplastic polyp (study 1) and T1b from Tis/T1a cancer (study 2). The agreement between the endocyto-pathological and conventional histopathological diagnosis was 100% (95%CI: 94.0%-100%) in study 1 and 100% (94.0%-100%) in study 2. The interobserver agreement among the three gastrointestinal pathologists was 100%, and the κ coefficient was 1.00 in both studies.

DISCUSSION

To our knowledge, this is the first report of a new clinical application of the endocytoscope for histopathological specimens. The quality of endocyto-pathological images taken by an endoscopist was sufficiently high to make a histopathological diagnosis. We attempted to take pathological images of histopathological specimens by conventional magnifying endoscopy (x 85 maximum optical magnification with approximately 2mm of a minimum depth of observation); however, cytological findings could not be evaluated owing to a lack of resolution power and focus depth. In contrast, the endocytoscope easily enables the evaluation of cytological findings by taking ultra-high power magnification images with contact on the histological slides. For better quality, the specimens were placed horizontally in a white container filled with water to control the diffuse reflection of the diffuse reflection of the scope light.

Linking endoscopic and histopathological images is a clinically essential step for endoscopists to improve endoscopic diagnosis for estimating the histopathology of gastrointestinal lesions. In situations where pathologists are scarce, it would be better to have endoscopists obtain histopathological images using a microscope. However, most endoscopists do not have microscopes in their institutions or are generally unfamiliar with using them. In this context, we considered it meaningful to have endoscopists obtain histopathological images using endocytoscopes. Additionally, our endocyto-pathological images have the advantage of being stored with endoscopic images in the same endoscopic system, which is helpful when holding clinicopathological conferences. We believe the endocyto-pathological diagnosis will reduce the growing burden on histopathologists, including their time and cost, when especially made with the CAD system. Further studies will be required to prove the hypothesis.

This study has limitations. First, knowledge of histopathology is required for endoscopists to take diagnosable ultra-high magnification images, especially for cancer depth diagnosis. Taking inadequate images would lead to the wrong endocyto-pathological diagnosis. Second, endocytoscopes have not yet been disseminated worldwide. However, the results of this study may encourage the spread of the endocytoscopes, especially in countries with a few pathologists.

Table 1 The agreement between endocyto-pathological and conventional histopathological diagnosis for differentiating low-grade adenoma from hyperplastic polyp by three gastrointestinal pathologists

	Conventional pathological diagnosis	
	Low-grade adenoma (*n* = 30)	Hyperplastic polyp (*n* = 30)
Endocyto-pathological diagnosis		
Low-grade adenoma	30	0
Hyperplastic polyp	0	30

Table 2 The agreement between endocyto-pathological and conventional histopathological diagnosis for differentiating T1b from Tis/T1a cancer by three gastrointestinal pathologists

	Conventional pathological diagnosis	
	T1b cancer (*n* = 30)	Tis/T1a cancer (*n* = 30)
Endocyto-pathological diagnosis		
T1b cancer	30	0
Tis/T1a cancer	0	30

CONCLUSION

In conclusion, endocyto-pathological images of colorectal lesions were adequate and reliable materials for histopathological diagnosis. Endocytoscopes will be disseminated in the future and have the potential for endocyto-pathology worldwide.

ARTICLE HIGHLIGHTS

Research background

Based on the background of the shortage of histopathologists, we explore the new application of endocytoscope for directly observing histopathological specimens of colorectal lesions and storing them as endocyto-pathological images with their endoscopic images.

Research motivation

Endocyto-pathological images taken by endoscopists potentially reduce the burden of histopathologists and facilitate holding clinicopathological conferences more simply.

Research objectives

To assess the feasibility of endocyto-pathological images taken by an endoscopist as adequate materials for histopathological diagnosis.

Research methods

This was a single-center prospective pilot study. Three gastrointestinal pathologists were asked to diagnose 40 cases of endocyto-pathological images of colorectal specimens (Each case contained seven images: one loupe image, three low-magnification images, and three ultra-high magnification images). The participants chose hyperplastic polyp or low-grade adenoma for 20 cases of endocyto-pathological images (10 hyperplastic polyps, and 10 Low-grade adenomas in conventional histopathology) in study 1 and high-grade adenoma/shallow invasive cancer or deep invasive cancer for 20 cases [10 tumor in situ (Tis)/T1a and 10 T1b] in study 2.

Research results

Agreement between the endocyto-pathological and conventional histopathological diagnosis by the three gastrointestinal pathologists was 100% (95%CI: 94.0%–100%) in studies 1 and 2. The interobserver agreement among the three gastrointestinal pathologists was 100%, and the κ coefficient was 1.00 in both studies.

Research conclusions

Endocyto-pathological images were adequate and reliable materials for histopathological diagnosis.

Research perspectives

Endocyto-pathological images taken by endoscopists will reduce the growing burden on histopathologists, including their time and cost, when especially used with the computer-aided diagnosis system.

FOOTNOTES

Author contributions: Inoue F, Hirata D, Iwatate M, Hattori S, Fujita M, Sano W and Sano Y contributed to the study concept and design; Sugai T, Kawachi H and Ichikawa K contributed to read endocytopathological images; Inoue F, Hirata D, Iwatate M and Sano Y contributed to the data analysis and interpretation; Inoue F contributed to draft the manuscript; and Sugai T, Kawachi H, Ichikawa K and Sano Y contributed to the critical revision of the manuscript for intellectual content.

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CASE REPORT

Hidden local recurrence of colorectal adenocarcinoma diagnosed by endoscopic ultrasound: A case series

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Abstract

BACKGROUND

Almost half of the patients with colorectal cancer (CRC) will experience local-regional recurrence after standard surgical excision. Many local recurrences of colorectal cancer (LRCC) do not grow intraluminally, and some may be covered by a normal mucosa so that they could be missed by colonoscopy. Early detection is crucial as it offers a chance to achieve curative reoperation. Endoscopic ultrasound (EUS) is mainly used in CRC staging combined with cross-section imaging study. EUS can provide an accurate assessment of sub-mucosal lesions by demarcating the originating wall layer and evaluating its echostructure. EUS fine-needle aspiration (FNA) provides the required tissue examination and confirms the diagnosis.

CASE SUMMARY

We report a series of five cases referred to surveillance for LRCC with negative colonoscopy and/or negative endoscopic biopsies. EUS-FNA confirmed LRCC implanted deep into the third and fourth wall layer with normal first and second layer.

CONCLUSION

Assessment for LCRR is still problematic and may be very tricky. EUS and EUS-FNA may be useful tools to exclude local recurrence.

Key Words: Colorectal cancer; Endoscopic ultrasound; Local recurrence; Fine-needle aspiration; Deep implanted CRC; Case report

Core Tip: The local recurrence of colorectal adenocarcinoma that has been implanted deeply in the submucosal layers is usually missed by colonoscopy, despite that some cases show submucosal elevation. Endoscopic biopsies often give negative results, so endoscopic ultrasound fine-needle aspiration can be used to confirm the diagnosis and give patients a better chance for proper management.

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INTRODUCTION

In patients with curatively resected colorectal cancer (CRC), local recurrence is often considered a clinical dilemma difficult to treat, may cause markedly disabling symptoms, and usually has a bad prognosis[1,2]. Several factors were incriminated in the recurrence as positive surgical margins, especially with inadequate excision, inadequate nodal dissection, implantation of exfoliated malignant cells into the deep layers, and changed biological characters at the site of large bowel anastomosis[3]. However, while colonoscopy remains the gold standard method of detecting local recurrences of colorectal cancer (LRCC) and metachronous lesions, it is considered an imperfect tool even in the best hands, with missing rates of adenocarcinoma ranging from 1% to 3%[4,5]. Unfortunately, not all local recurrences are detectable at the mucosal surface with false-negative colonoscopy. In these cases, endoscopic ultrasound (EUS) plays an irreplaceable role allowing highly detailed visualization of all the bowel wall layers with all the surrounding structures[6].

The great value of EUS in the evaluation for possible CRC recurrence nowadays comes from its ability to direct fine-needle aspiration (FNA) and fine needle biopsy, thus allowing the acquisition of tissue samples for histological and immunohistochemical examination, and providing a definitive diagnosis.

There are two studies on EUS FNA that showed its high accuracy in the diagnosis of subepithelial and extra-luminal lesions of the colon and rectum[7,8]. In both studies, the accuracy of EUS-FNA was 90%-95% compared with an 82% accuracy for imaging alone[8].

CASE PRESENTATION

All patients gave their informed written consent before the procedure. All patients had MRI examination before EUS examination.

All examinations were done under deep sedation with IV propofol. All cases had ano-rectal lesions, maximum 15-20 cm from the anal verge, which are easy to be scanned by the side view scope. No right hemicolon masse were included as they are very difficult to be approached by the side view scope. For EUS-FNA, we used Cook 22G needles (Echotip, Wilson-Cook) (Figure 1).

Chief complaints

Case 1: This was a 70-year-old male patient. During LRCC surveillance, no lesions were detected by colonoscopy. The patient experienced unexplained weight loss and was referred for EUS assessment.

Case 2: This was a 45-year-old male patient. LRCC surveillance colonoscopy revealed a submucosal lesion at the rectal anastomotic line, and multiple endoscopic biopsies got negative results repeatedly. The patient was referred for EUS examination.

Case 3: This was a 45-year-old female patient who presented with difficult defecation. Colonoscopy revealed narrowed rectal anastomotic line, but biopsies were negative.

Case 4: This was a 48-year-old male patient. During LRCC surveillance, submucosal elevation at the sigmoido-colonic anastomotic line was noticed by colonoscopy, and endoscopic biopsies showed

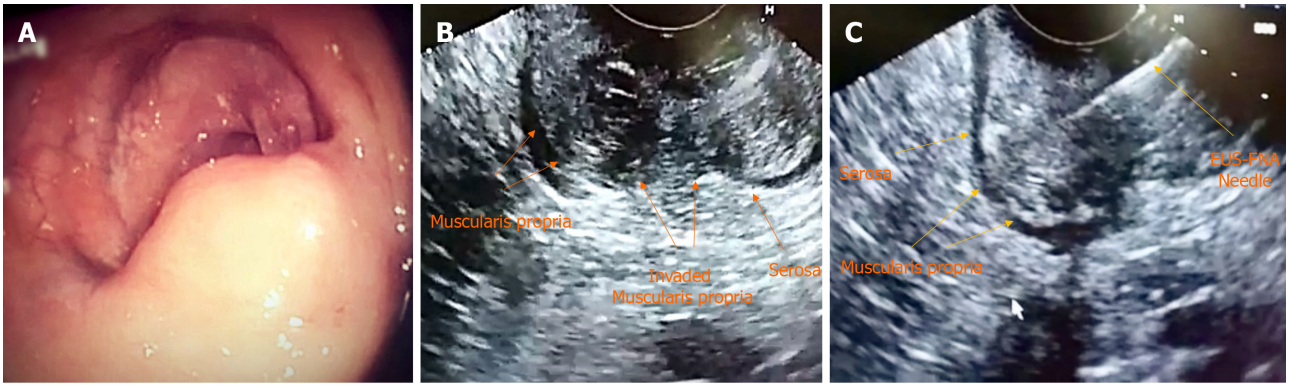

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Figure 1 Colonoscopy and endoscopic ultrasonography. A: Colonoscopic appearance of submucosal lesion at the anastomotic line at the recto-sigmoid junction; B: Endoscopic ultrasound appearance of a hypoechoic mass arising from the 3rd layer with interruption of the fourth layer at its base; C: Endoscopic ultrasound guided fine-needle aspiration acquisition. EUS: Endoscopic ultrasound; FNA: Fine-needle aspiration.

negative results.

Case 5: This was a 46-year-old male patient. During LRCC surveillance, colonoscopy showed a submucosal lesion with negative endoscopic biopsies.

History of present illness

Case 1: The patient experienced unexplained weight loss and was referred for EUS assessment.

Cases 2, 4, and 5: The patients underwent LRCC surveillance.

Case 3: The patient presented with difficult defecation.

History of past illness

Cases 1-5: The patients had a history of CRC surgical excision.

Personal and family history

Cases 1-5: No notable personal or family medical history.

Physical examination

Case 1: Unremarkable apart from unexplained weight loss.

Cases 2-5: Unremarkable physical examination.

Laboratory examinations

Case 1: No other abnormalities were noted apart from mild microcytic hypochromic anemia.

Cases 2-5: No other abnormalities noted.

Imaging examinations

Case 1: EUS assessment revealed a 2.8 cm × 4 cm homogenous mass at the rectal anastomotic line, arising from the fourth wall layer. FNA was performed, and pathological examination confirmed adenocarcinoma.

Case 2: EUS examination showed a 1.9 cm × 2.9 cm homogenous mass, arising from the fourth layer. FNA was performed, and pathological assessment confirmed adenocarcinoma recurrence.

Case 3: EUS was conducted and revealed a homogeneous mass measuring 3 cm × 3.3 cm, arising from the fourth layer. FNA was carried out, and adenocarcinoma local recurrence into the deep submucosal layers confirmed.

Case 4: EUS revealed a heterogeneous mass measuring 2.3 cm × 4.2 cm arising from the third layer. FNA was performed, and pathological studies confirmed adenocarcinoma recurrence.

Case 5: EUS was carried out and revealed a 1.2 cm × 2.4 cm homogeneous mass, arising from the fourth layer at the ano-rectal anastomotic line. FNA was performed, and the result confirmed adenocarcinoma.

FINAL DIAGNOSIS

We report five case series referred to surveillance for LRCC with negative colonoscopy and/or negative endoscopic biopsies. EUS-FNA confirmed LRCC implanted deep into the third and fourth wall layer with normal first and second layer.

TREATMENT

Case 1: The patient underwent Lt hemi-colectomy for local recurrence and was referred to medical oncology.

Case 2: Partial colectomy was carried out.

Case 3: The patient received chemotherapy for cancer colon.

Case 4: The patient was referred to medical oncology.

Case 5: The patient received chemo-radiotherapy for ano-rectal cancer.

OUTCOME AND FOLLOW-UP

In all cases, the patients were referred to medical cancer institute.

DISCUSSION

CRC is one of the common and lethal malignancies worldwide and is considered the second leading cause of cancer deaths in the United States[9]. Most of CRC patients underwent surgical excision aiming at curative treatment, and up to 40% of patients with the locoregional disease will develop recurrent cancer, of which 90% will occur within 5 years[10,11].

The postoperative surveillance of patients treated for CRC is a clinical challenge, first due to distorted anatomy and scarring and second because of intent to prolong survival by diagnosing recurrent and metachronous cancers at a curable stage. LRCC surveillance strategies combined different modalities, including clinical assessment, tumor marker carcinoembryonic antigen, computed tomography (CT) scans, and endoluminal imaging, including colonoscopy, sigmoidoscopy, EUS, and CT colonography. The optimal surveillance strategy is still not clearly defined.

A number of studies have shown EUS to be very accurate in detecting LCRR, with EUS-FNA being able to provide tissue confirmation[12,13].

Several guidelines and organizations recommend EUS in post-treatment surveillance for resected colon and rectal cancer. The NCCN guidelines state that flexible sigmoidoscopy with EUS or MRI should be done every 3 to 6 mo for 2 years, then every 6 mo to complete 5 years for patients with rectal cancer undergoing transanal excision only[14]. The United States Multi-Society Task Force include EUS as an alternative to sigmoidoscopy in the testing strategy for patients at higher risk of recurrence[15].

In patients with a curative resection for rectal cancer, the current US Multi-Society Task Force recommendation suggests EUS at 3-6 mo for the first 2 years after resection as a reasonable option[16]. It is noteworthy that not all recurrences are evident at the mucosal surface, so in those cases the benefit of EUS will be restricted in highly detailed visualization and assessment of all the bowel wall layers with all the surrounding structures[6].

Our study showed a rare clinical scenario of hidden implanted adenocarcinoma in the third and fourth layer with an intact mucosal layer, so it was not evident intraluminally and missed by colonoscopy, and endoscopic biopsies were false-negative repeatedly. This may be explained by the presence of cancer cells at the anastomotic line or trapping of cancer cells in the staple line, resulting in local recurrence, especially in patients who underwent double-staplinganastomosis[6,17].

Therefore, EUS-FNA gained the optimal diagnostic procedure and defined the proper treatment plan.

EUS can act not only as a method for the evaluation of precancerous polyps and subepithelial lesions found during screening of CRC, but also it has a great role in follow-up after resection of rectal carcinoma for early detection and tissue confirmation of locally recurrent cancer colon, by allowing the collection of specimens for histological and immuno-histochemical analysis, and overcoming some of the inherent user bias[18].

CONCLUSION

Assessment for LCRR is still problematic and may be very tricky, so we recommend using EUS-FNA to exclude local recurrence, since it could be deeply implanted and missed by routine imaging tools and colonoscopy.

FOOTNOTES

Author contributions: Wahba M and Abdellatif AA were involved equally in writing the manuscript; Fontagnier E and Hagag H were involved equally in collecting the data; Elenin SA read and revised the manuscript; Okasha HH revised and approved the final manuscript; all authors have read and approved the final manuscript.

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LETTER TO THE EDITOR

Laparoscopic and endoscopic cooperative surgery for full-thickness resection and sentinel node dissection for early gastric cancer

Serafino Vanella, Maria Godas, Joaquim Costa Pereira, Ana Pereira, Ivano Apicella, Francesco Crafa

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Abstract

The endoscopic submucosal dissection (ESD) technique has become the gold standard for submucosal tumors that have negligible risk of lymph node metastasis (LNM), due to its minimal invasiveness and ability to improve quality of life. However, this technique is limited in stage T1 cancers that have a low risk of LNM. Endoscopic full thickness resection can be achieved with laparoscopic endoscopic cooperative surgery (LECS), which combines laparoscopic gastric wall resection and ESD. In LECS, the surgical margins from the tumor are clearly achieved while performing organ-preserving surgery. To overcome the limitation of classical LECS, namely the opening of the gastric wall during the procedure, which increases the risk of peritoneal tumor seeding, non-exposed endoscopic wall-inversion surgery was developed. With this full-thickness resection technique, contact between the intra-abdominal space and the intragastric space was eliminated.

Key Words: Endoscopic submucosal dissection; Laparoscopic endoscopic cooperative surgery; Non-exposed endoscopic wall-inversion surgery; Early gastric cancer; Nodal basin evaluation

Core Tip: The initial indication for laparoscopic endoscopic cooperative surgery (LECS) was gastric submucosal tumors (SMTs) without ulcerative features. Later, the LECS procedure was expanded to include gastric SMTs with ulceration and gastric cancer (GC) with negligible risk of lymph node metastasis. Currently, LECS can be applied to early GC in which sentinel node (surgical nodal basin) dissection can be performed with intra-operative evaluation by one-step nucleic acid amplification. Modified LECS procedures have been developed, such as inverted LECS, non-exposed endoscopic wall-inversion surgery, a combination of laparoscopic and endoscopic approaches to neoplasia with a non-exposure technique, and closed LECS.

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TO THE EDITOR

We read with great interest the retrospective study by Inokuchi *et al*[1], which evaluated the feasibility and efficacy of gastric endoscopic submucosal dissection (ESD) in patients aged ≥ 80 years. The study was based on 172 sessions of gastric ESD in 124 patients, with a final diagnosis of gastric cancer (GC) in 175 Lesions. The patients were studied retrospectively to evaluate short-term outcomes (procedure-related mortality, complications, curative dissection and rates of *en bloc* dissection) and survival. In the study, there was a high *en bloc* dissection rate (97.1%) and a curative dissection rate of 77.1%. Complications occurred in 8 patients (4.7%). There were 6 cases (3.4%) of postoperative bleeding, 2 (1.1%) of intraoperative perforation, and 1 (0.6%) of aspiration pneumonitis after ESD. There were no procedure-related deaths[1]. The significant risk factors that increased the rates of bleeding were tumor location in the lower third of the stomach, lesions > 40 mm, presence of a depressive component, and ulcerative features. The main risk factor for perforation was the site in the upper third of the stomach[1]. To evaluate long-term outcomes, the patients were divided into two groups: curative group (n = 87) and non-curative (without additional surgery) ESD group (n = 33). The overall survival rate was strongly predicted by the Charlson Comorbidity Index (CCI). Patients with CCI ≥ 2 had a poor prognosis, regardless of curability. The conclusion of the study underlines that ESD is feasible even in elderly patients aged > 80 years, without an increase in complications.

It is clear why, over the years, the ESD technique has become the gold standard for submucosal tumors with negligible risk of lymph node metastasis (LNM), namely its minimal invasiveness and ability to improve quality of life. We agree with the importance of ESD, but this technique is limited in stage T1 cancers that have a low risk of developing LNM.

The laparoscopic endoscopic cooperative surgery (LECS) approach was melt, for the treatment of gastric submucosal tumors (SMTs), from fusion of ESD and surgery to endoscopic identification of the resection line and laparoscopic resection of gastric wall[2-4]. LECS begins with the endoscopic pre-cut around the tumor and section of the gastric wall. Then, with a laparoscopic approach, the tumor is excised and the gastric wall defect is reconstructed with a mechanical stapler. The advantage is that there are no limitations on tumor location[5]. LECS was used initially for the SMTs without ulceration [6]. Subsequently, the indication was expanded to also include lesions with ulcerative features and GC with very low risk of LNM[7,8]. The limitation of classical LECS includes the possibility of tumor and gastric content contamination into the peritoneal cavity because of the opening of the gastric wall during the procedure, increasing the risk of peritoneal tumor seeding. Therefore, some modified LECS procedures have been developed, such as inverted LECS[7], non-exposed endoscopic wall-inversion surgery (NEWS)[9-11], a combination of laparoscopic and endoscopic approaches to neoplasia with a non-exposure technique[12], and closed LECS[13].

The NEWS technique allows full thickness resection avoiding contamination of the intra-abdominal region with intragastric material.This procedure does not require intentional perforation, avoiding the risk of tumor seeding. Saline solution is injected endoscopically into the submucosa to mark the lesion margins. In the next step, the section of the outer layers of the wall and their suture are performed laparoscopically in such a way as to invert the early GC (EGC) towards the inside of the stomach. The last step is represented by the removal of the specimen by the ESD approach and closure of the defect with clips or nets. NEWS has the advantage of avoiding peritoneal contamination and cancer cell seeding. The limitations are represented by the long duration due to the combination with ESD and endoscopic closure of the mucosal defect. It is also difficult to perform for lesions of the esophagogastric junction and pylorus. The main disadvantage of this technique is the size of the tumor. Since the lesion must be extracted orally, this approach is limited for gastric SMTs greater than 3 cm[5]. The indication

for NEWS is gastric SMTs and lymph node-negative EGC, where there is some technical contraindication to ESD.

The Japanese National Health Insurance Plan recently approved the LECS procedure for GC for insurance coverage. Postoperative gastrectomy syndrome and post-procedure physical weakness are negligible with LECS.

LECS was recently performed in an elderly patient who refused radical surgery as a palliative treatment[14].

Currently, the main indications for modified LECS are EGCs not amenable to endoscopic treatment by endoscopic mucosal resection (EMR)/ESD, again with negligible risk of LNM. The suspicion of LNM requires a gastrectomy with lymphadenectomy[15].

The combination of the NEWS technique with sentinel node (SN) navigation surgery for the treatment of EGCs was reported by Goto *et al*[10,16]. A previous prospective multicenter study had already validated SN navigation surgery for GC[17]. The combined use of modified LECS and SN navigation surgery in the case of EGC allows for oncologically adequate resections with minimally invasive approaches, and can represent a valid alternative in elderly patients. Currently, this combination technique can be applied to EGC in which SN (surgical nodal basin) dissection can be performed with intra-operative evaluation by the one-step nucleic acid amplification assay[8].

Moreover, as suggested by the authors, this new cooperative technique can be applied even to EGC, which has features that significantly increase the risk of bleeding and/or perforation. Careful selection of indications and careful post-operative follow-up is required. No cases of disseminated GC recurrence have been described after LECS[7,15,18,19]. Randomized clinical trials on long-term oncological outcomes are needed to better clarify the future indications of ESD and modified LECS with SN navigation surgery.

FOOTNOTES

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The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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MINIREVIEWS

Simulation-based mastery learning in gastrointestinal endoscopy training

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Abstract

Simulation-based mastery learning (SBML) is an emerging form of competency-based training that has been proposed as the next standard method for procedural task training, including that in gastr-ointestinal endoscopy. Current basic gastrointestinal endoscopy training relies on the number of procedures performed, and it has been criticized for its lack of objective standards that result in variable skills among trainees and its association with patient safety risk. Thus, incorporating simulators into a competency-based curriculum seems ideal for gastrointestinal endoscopy training. The curriculum for SBML in gastrointestinal endoscopy is currently being developed and has promising potential to translate into the clinical performance. Unlike the present apprenticeship model of "see one, do one, teach one," SBML integrates a competency-based curriculum with specific learning objectives alongside simulation-based training. This allows trainees to practice essential skills repeatedly, receive feedback from experts, and gradually develop their abilities to achieve mastery. Moreover, trainees and trainers need to understand the learning targets of the program so that trainees can focus their learning on the necessary skills and trainers can provide structured feedback based on the expected outcomes. In addition to learning targets, an assessment plan is essential to provide trainees with future directions for their improvement and ensure patient safety by issuing a passing standard. Finally, the SBML program should be planned and managed by a specific team and conducted within a developed and tested curriculum. This review discusses the current state of gastr-ointestinal endoscopy training and the role of SBML in that field.

Key Words: Simulation training; Education; Endoscopy; Mastery learning; Competency-

based education; Curriculum

Core Tip: The traditional apprenticeship model for gastrointestinal training has been widely criticized for its lack of standards and patient safety risks. Thus, the basic gastrointestinal endoscopy training method needs to be revised from the apprenticeship model to a simulation-based mastery learning (SBML) model, which relies on specific learning objectives with the integration of simulators. SBML is a competency-based training method aimed at creating highly competent trainees and reducing differences in skills among them. The present review discusses the current state of gastrointestinal endoscopy training, the role of SBML in that field, and recent experiences and future prospects of SBML.

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INTRODUCTION

Endoscopy is the gold standard technique for the diagnosis of various gastrointestinal (GI) tract diseases and also allows examiners to directly provide therapeutic interventions if needed. This procedure is performed by a trained gastroenterologist or endoscopic surgeon. The need for endoscopic procedures is projected to increase every year due to the growing prevalence of GI diseases and technical improvements in GI endoscopy[1]. Most GI endoscopy training still follows the traditional apprenticeship model of "see one, do one, teach one." This model relies on the number of exposures to procedural caseloads, which causes varying results among trainees[2]. This lack of a standardized curriculum has recently come under intense scrutiny because it is associated with patient safety risks, as trainees cannot safely perform a medical procedure after having observed it only once[3].

A mastery learning model is an approach to competency-based training, in which participants must acquire specific skills before moving on to the next stage of training. The basic principle of mastery learning is that all participants can achieve the highest standard of learning objectives with the minimum possible variation in results. Meta-analyses show that mastery learning significantly leads to skill improvement, has a moderate effect on patient outcomes compared to the traditional apprenticeship method, but might demand more time than other methods. Mastery learning-based training provides consistent positive results and has a beneficial effect on both patient care and the budget spent during the training process[4].

A simulation-based training (SBT) method has been also proposed as an alternative to replace the old teaching method. The use of simulators to acquire psychomotor abilities has been widely studied and recommended by leading educational institutions. With a SBT method, trainees can achieve procedural competence without compromising patient safety, particularly in those procedures that require practical experience and visual-spatial skills[5]. Additionally, skills of the operator can be improved and the length of the procedure reduced by using a simulator. Finally, simulators can also be used to evaluate trainee progress[6].

SBT and mastery learning methods have several benefits over the traditional apprenticeship model. This article reviews the role of simulation-based mastery learning (SBML) in GI endoscopy and describes the planning and management for the implementation of this model, including experiences regarding its application.

DEVELOPMENT OF GI ENDOSCOPY TRAINING

Since 1962, the American Society for Gastrointestinal Endoscopy has held symposiums about teaching methods in GI endoscopy and later formed a formal endoscopy training program. Along with the development of science and advancement in the complexity of endoscopic procedures, gastroenterological education began to be developed independently as part of a subspecialty of internal medicine[4]. The development of specific training in endoscopy and gastroenterology also impacted the education period for this field, which initially consisted of 1 year to 2 years and then was extended to 3 years[4]. Currently, there is no global standardization of the gastroenterology education length. Some countries, such as the Netherlands, are now expanding their gastroenterology curriculum to 3 years to 4 years,

starting with 2 years of general internal medicine training[7,8]. In Korea, endoscopy training is conducted for 1 year to 2 years during a gastroenterology fellowship program[9]. Meanwhile, in Japan, a physician must complete 3 years of internal medicine residency and 5 years of gastroenterology fellowship to become a board-certified endoscopist[10]. The World Gastroenterology Organization states that a student must complete 3 years of internal medicine residency before pursuing gastroenterological-specific education and training for the next 3 years[11].

The current state of endoscopy training is defined by the conventional apprenticeship model, with a strong emphasis on case/procedure volume and without a formal curriculum. Trainees are usually assigned the minimum number of cases or procedures they need to achieve competency or practical eligibility. The duration of the training program is commonly fixed, and an assessment is conducted near the end of the program. This training method has potential variability in terms of skill outcomes. As trainees might be overwhelmed at the start of the program, the initial cases they encounter can be ineffective for learning. A European survey showed significant differences in various gastroenterology training among 16 European countries, ranging from the minimum number of procedures required, training period, form of supervision to whether some interventional procedures were performed[12]. Recently, curriculum-based medical education (CBME) has recently been proposed to improve endoscopy training. The CBME model includes The American Society of Gastrointestinal Endoscopy Skills, Training, Assessment, and Reinforcement program with a curriculum that combines hands-on training, formative feedback, and postcourse skills and knowledge assessments[13].

One of the learning methods that has been developed for endoscopy training is a simulated-based approach. Endoscopy simulator models have continued to be developed and advanced in the last decades, ranging from mechanical simulators, animal model simulations, and computer simulators[14]. The evolution of endoscopy simulators is described in Table 1. These developments provide opportunities for trainees to learn various diagnostic and therapeutic techniques. Generally, these simulators use an endoscope that is inserted into a mannequin. Consequently, trainees can be more familiar with endoscopic procedures and be able to practice them on an actual patient. Some advanced computer simulators also provide a realistic picture on the monitor and can simulate a patient's response. The computer simulator also combines training to learn hand-eye coordination, recognition of pathological features, and immediate feedback output[15]. A systematic review showed that skills acquired from SBT were transferable to the clinical setting, as participants of SBT scored higher global assessment scores and fewer errors[16]. Moreover, forms of simulation that can be considered in endoscopy training include the following[17-24].

Patient simulation: A simulated mannequin that resembles a human with respiration, pulse, and other vital signs is used. This type of simulation can be used for simple physical examination scenarios.

Clinical environment simulation: In this simulation, a room that resembles an actual clinical practice room, for example, an operating room, is prepared. Thus, trainees become more familiar with the actual situation.

Virtual procedure simulation: These simulations have equipment relevant to the procedure, such as esophagogastroduodenoscopy or colonoscopy, and can also present various disease scenarios according to the needs of trainees.

Electronic medical record simulation: This simulation uses artificial data about cases, including disease history and laboratory results, which can be integrated with other systems.

MASTERY LEARNING IN GI ENDOSCOPY

Mastery learning is a form of competency-based training in which trainees have to achieve specific skills or be deemed good enough to perform a procedure before moving on to the next stage of training. Competence is the minimum level of skill, knowledge, or expertise acquired through training necessary to perform a task or procedure and to ensure that safe and technically successful procedures are carried out and that observations and results are accurate[25,26]. Mastery learning focuses on the trainees instead of the patient. The old teaching has resulted in inconsistent teaching, testing, and retention of skills, while mastery learning demands trainees to acquire and maintain specific skills and knowledge through deliberate practice without time limit. Deliberate practice consists of nine elements: highly motivated learners with good concentration, clear learning objectives, an appropriate difficulty level, repetitive practice, rigorous measurements, informative feedback, monitoring and error correction, performance evaluation, and advancement to the next task[27]. Mastery learning effectively develops both therapeutic skill and high self efficacy to utilize the skill[28].

Mastery of basic endoscopic techniques is essential for every endoscopist, because if the procedure is performed incorrectly, it can cause severe complications that might threaten the condition of patients. The essential steps of endoscopy are endoscope insertion, precise observation, and appropriate imaging [29]. Skills developed by each endoscopist may vary and are influenced by differences among supervisors during the procedure. Hence, standardized training is necessary to maintain the competence of trainees[30].

Table 1 Development of endoscopy simulators

Ref.	Developer	Yr	Characteristics
Telleman *et al*[19], 2009	Erlangen-Nuremberg University Clinic	1974	An anatomical model of the esophagus, stomach, and duodenum used to train for endoscopic maneuvers
Williams *et al*[20], 2000	Imperial College/St Mark's Hospital	1980	An anatomical model of the colon to train for angling maneuver in the organ
			Constant supervision is needed because trainees could damage the endoscope by excessive maneuvering
			The appearance of the colon surface is not realistic in the model
Classen and Ruppin [21], 1974	Imperial College/St Mark's Hospital	1980	More realistic control compared to previous models as the endoscope can be rotated, and endoscope insertion and withdrawal can be detected
			Integrated with a monitor showing live simulation
			The length of the endoscope that can be inserted is limited
Williams *et al*[22], 1990	Imperial College/St Mark's Hospital	1985	The endoscope can be fully inserted
			A sensation of resistance and an audio simulation that mimics patient's complaints are included
			Still unrealistic
Long and Kalloo[15], 2006	Immersion Medical	2001	Provides an opportunity to practice various procedures, including biopsy
			Provides immediate feedback
			Realistic simulation as a sensation of resistance and contraction is included
Koch *et al*[23], 2008	Simbionix	2008	Provides realistic simulation
			Can be used to practice endoscopic maneuvers
			Can distinguish between the ability level of endoscopy experts and intermediate level
Triantafyllou[24], 2014	CAE Healthcare	2013	Can be accompanied by the patient's history and various clinical parameters that can change during the endoscopy by the participant
			Combines endoscopic procedures with virtual backgrounds

Traditionally, competence in endoscopy is acquired after completing a specific number of recommended procedures based on expert opinions published by medical gastroenterology societies or associations, as described in Table 2. However, according to the aforementioned mastery learning principles, competence cannot be determined only by the number of procedures performed. A defined and detailed assessment tool should be incorporated to objectively assess trainees to deliver high-quality care[31].

To ensure competence in mastery learning, two aspects are needed: training and subsequent assessment by endoscopy experts or trainers. Through this training, trainees acquire the necessary technical and cognitive skills[25]. Examples of technical and psychomotor skills associated with endoscopy include scope handling and strategies for scope advancement, loop reduction, recall, and mucosal inspection. Cognitive competence reflects knowledge acquired about endoscopy and its application in clinical practice. Cognitive skills include choosing the most appropriate endoscopy test to assess and treat clinical problems, recognizing the lesion, and managing sedation. Crucial integrative competencies to endoscopy include decision-making, teamwork, communication, leadership, awareness of the situation, professionalism, and patient safety awareness[26].

Based on the psychological aspect, three factors underlie mastery learning: Behavioral development, constructive learning, and social cognition. Behavioral development pursues the acquisition and maintenance of technical and communication skills. Clinical thinking, community approach, ethics, advocacy, and regular self-reflection aim to shape social and cognitive constructs. Social cognition is a prerequisite for professionalism. These three aspects support the formation of SBML, which includes a curriculum design to set learning objectives[32-37].

SIMULATION-BASED TRAINING IN GI ENDOSCOPY

The SBML method uses an instructional approach, meaning that trainees must have a certain level of competence in a simulated environment before performing procedures on actual patients[24]. With this method, trainees progress through different simulations with increasing difficulty. SBML provides opportunities for students to practice as often as possible to improve their performance before operating

Table 2 Minimum number of trainings needed to achieve competence in different procedures according to gastroenterology associations

Source	EGD	Colonoscopy	ERCP
European Diploma of Gastroenterology[32]	300	100	150
ASGE[33]	130	140	200
SAGES[34]	35	50	-
Korean Society of Gastrointestinal Endoscopy[35]	1000	150	30
British Society of Gastroenterology[36]	300	100	150

ASGE: American Society for Gastrointestinal Endoscopy; EGD: Esophagogastroduodenoscopy; ERCP: Endoscopic retrograde cholangiopancreatography; SAGES: Society of American Gastrointestinal and Endoscopic Surgeons.

on patients. This method can optimize clinical outcomes and reduce the risk of complications or other hazards for patients that may occur during the operation period of a novice endoscopist[17,38]. In addition, SBML can minimize variations between trainees upon completion of the program[24,39].

Several studies in other fields of medical procedural training have shown the benefits of SBT and mastery learning over the traditional apprenticeship model. A meta-analysis by Harrison *et al*[40] included 14 studies involving 633 trainees in cardiology procedures and found that SBT followed by structured training provided superior results than traditional methods. The quality of patient care and patient feedback obtained by this method were better than those obtained by a conventional training approach. A meta-analysis by Cook *et al*[41] included 82 studies evaluating SBML in procedural settings such as surgeries and airway management. They found that SBML was significantly better at improving procedural skills than traditional methods but might takes more time. A systematic review on patient outcomes in simulation based medical education also reported small to moderate patient benefits in comparison with no intervention[38]. A study published in 2014 revealed the effectiveness of colonoscopy training with virtual simulation in the early learning curve of novices. Performance improvements were also found later during patient-based colonoscopy[42]. Another multicenter study found higher objective competency rates during the early phase of colonoscopy training[43].

A prospective randomized study that evaluated the diagnostic abilities of trainees using upper GI endoscopy concluded that structured SBT was superior to SBT or clinical training alone. This study also found that the use of the simulator was valuable as the first step in developing diagnostic skills to perform upper GI endoscopy, but it was not sufficient to ensure the overall competencies[30]. Several reports on SBT for GI endoscopy are described in Table 3.

Generally, studies on SBT in GI endoscopy training have shown favorable results, especially in the early phase of training, as it reduces the time required to reach technical competence and the number of endoscopic procedures needed to perform it independently. With SBT, trainees can perform the procedures and exercises repeatedly using a simulator. This repetition improves the cognitive and practical skills of students and allows them to become more acquainted with endoscopic features and settings. A meta-analysis showed that simulation can increase patient safety and decrease the risk of adverse events, as trainees are more skilled and familiarized with the clinical settings at the moment of performing the endoscopy[44-49]. It also provides an opportunity for trainees to learn at their own pace [50-54].

However, some systematic reviews have reported inconclusive evidence supporting SBT as a replacement for conventional training. SBT might be more beneficial as a supplement to conventional training, especially in the early phase. Nevertheless, reducing patient-based training in favor of SBT is not recommended as it cannot replace conventional patient-based training[48,51,52]. Hence, simulation must be accompanied by direct clinical experience with patients in order to understand the actual clinical setting[39]. A study conducted in 2004 found that simulation without feedback from experts did not improve the skills of trainees. Providing trainees access to a simulator cannot guarantee appropriate learning by itself. Therefore, SBT should be delivered purposefully within a developed curriculum to allow trainees to practice essential skills, receive feedback from experts, and develop skills gradually and appropriately to achieve mastery[55]. Feedback and debriefing are essential in SBT to allow trainees identify their weakness and improve their performance accordingly[56]. Simulation with a proper environment or scenario is also beneficial to the improvement of endoscopic non-technical skills such as communication and teamwork, situation awareness, leadership, judgment, and decision making[57]. A previous study showed that integrating endoscopic non-technical skills training improved novice trainees' performance and competency, which might benefit patients[58].

Table 3 Studies on simulation-based endoscopy training

Ref.	Study design	Methods	Conclusion
Ferlitsch *et al* [39], 2002	Prospective randomized trial	13 endoscopy trainees were divided into two groups: simulator training and no simulator training	Simulator-trained group had better skills, shorter scope insertion time, and fewer adverse events
Giulio *et al*[44], 2004	Prospective randomized trial	22 fellows with no experience in endoscopy were divided into two groups: preclinical training with computer-based simulator and no preclinical training	The first group performed a more complete procedure, required less assistance, and was assessed as better by the instructor
Cohen *et al*[43], 2006	Prospective randomized trial	45 1st-yr GI fellows were divided into two groups: unsupervised simulator training using GI mentor and no simulator	Fellows in the simulator group had significantly higher objective competency rates during the first 100 cases. Fellows who underwent GI mentor training performed significantly better during the early phase of real colonoscopy training
Shirai *et al*[45], 2008	Prospective randomized trial	10 trainees were divided into two groups: simulator and non-simulator	5 h of simulator training improved EGD performance
Ferlitsch *et al* [46], 2010	Prospective randomized trial	28 internal medicine residents were divided into two groups: simulator-trained before conventional training and conventional training only	Virtual simulator training improved technical accuracy during the early and mid-term phase of training, thus reducing the time needed to reach technical competency. However, the clinical effect is limited
Haycock *et al* [47], 2010	Prospective randomized trial	36 novice colonoscopists were divided into two groups: simulator training and patient-based training	Simulator-trained group performance matched the patient-based group performance, and showed superior technical skills on simulated cases
Ende *et al*[30], 2012	Prospective randomized trial	Residents with no previous experience in endoscopy were divided into three groups: clinical and simulator training, clinical training only, and simulator training only	First group showed better results than the other groups. Third group showed a shorter procedure duration
Qiao *et al*[48], 2014	Systematic review	Fifteen studies comparing virtual colonoscopy or gastroscopy training with other intervention were analyzed	Virtual endoscopy simulator training might be effective for gastroscopy, but no data are available for colonoscopy
Singh *et al*[49], 2014	Systematic review and meta-analysis	Thirty-nine articles, including twenty-one randomized trials on simulation-based training in gastrointestinal endoscopy were analyzed	Simulation-based training significantly enhanced the skills of trainees, reduced the time needed to finish a procedure, and improved patient outcomes
Ekkelenkamp *et al*[50], 2016	Systematic review	Twenty-three studies on simulator training and learning curves, including seventeen randomized controlled trials, were analyzed	Validated VR simulator training in the early phase accelerated the learning of practical skills. Assessment of performance level on GI endoscopy procedures should be done continuously with validated assessment tool, rather than threshold number
Mahmood *et al* [5], 2018	Systematic review	Twenty-one randomized controlled trials on VR simulation in endoscopy training were analyzed	VR simulation showed improved skills in all areas at the beginning of learning; nonetheless it was not effective as a replacement for conventional training
Khan *et al*[51], 2018	Systematic review	Eighteen trials on endoscopic procedures were analyzed	VR-based training in combination with conventional training showed superior result over VR training alone. Evidence was inconclusive regarding whether VR-based training can replace conventional training
Smith *et al*[52], 2021	Systematic review and meta-analysis	Twenty-four studies on simulation of EGD, colonoscopy, ERCP, flexible sigmoidoscopy, or hemostasis procedures were analyzed	Likely positive impact of simulation training on patient comfort, cecal and biliary intubation. However, studies on the effect of simulation training are small and have a short follow-up time
Zhang *et al*[53], 2021	Systematic review	Twenty-two studies on endoscopy VR simulation training were analyzed	VR simulation training resulted in comparable or significantly better performance than clinical training, no training, other types of simulation, and another form of VR

GI: Gastrointestinal; ERCP: Endoscopic retrograde cholangiopancreatography; EGD, Esophagogastroduodenoscopy; VR: Virtual reality.

EXPERIENCES IN SIMULATION-BASED MASTERY LEARNING FOR ENDOSCOPY TRAINING

Several studies have shown endoscopy mastery learning experiences. Nguyen-Vu *et al*[59] reported a 2-wk course for gastroenterology fellows at the University of California with no prior experience in endoscopy. They divided the learning period into two phases: the 1st week for learning the basics of endoscopy and the 2nd week for learning various therapies in endoscopy. These phases were further divided into specific endoscopic skills such as endoscopic tip control, image documentation, biopsy, and clip administration. Trainees were assigned readings and underwent online assessments before attending hands-on training with a simulator. They had to pass the competency assessment for a specific skill before moving to the next topic. This study showed that the SBML program could rapidly

help trainees acquire endoscopic skills through a comprehensive curriculum. Online reading and assessments enabled trainees to learn at their own pace, and using a simulator provided them with a chance to engage in repetitive practice. Dividing endoscopic skills also allowed trainees to focus on the specific skills they needed to refine.

Ritter *et al*[60] reported an endoscopy training system (ETS) using an SBML curriculum implemented with general surgery residents to pass the Fundamentals of Endoscopic Surgery (FES) skills examination. They divided ETS into five tasks which were organized in two tabletop units. The first unit included scope manipulation, tool targeting, and retroflexion tasks using a simple endoscopic tool. The second unit consisted of loop management and mucosal inspection tasks using a stylized body form. Most participants completed this simulation-based curriculum in less than 1 wk with more than 90 min of practice per day. This study suggested that the application of the SBML curriculum to flexible endoscopes provides significantly improved results on posttraining assessments compared with pretraining assessments. This study also found that after five sessions of SBT, participants could produce posttest scores equivalent to those of doctors who had performed 150-300 endoscopy procedures. This result implies that vast clinical experience is not needed to participate in the SBML program. The ETS was further developed by setting the training standards for the SBML curriculum, resulting in attainable standards that improved FES scores in the skills exam[61]. Another subsequent study published in 2021 evaluated the effect of SBML curriculum implementation early in residency. It revealed that early implementation of SBML curriculum for flexible endoscopy training resulted in comparable performance to those with high level of clinical endoscopic experience[62].

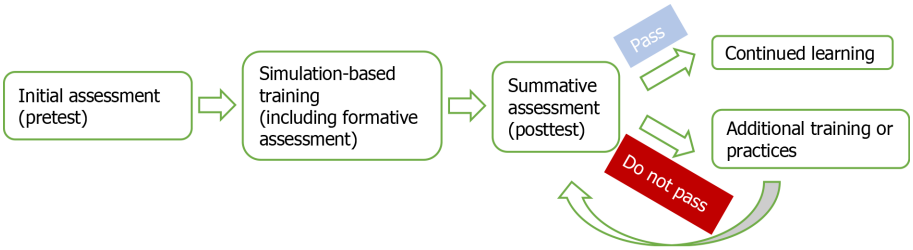
Soetikno *et al*[61] developed a 6-wk SBML program for 1st-year gastroenterology fellows of the Philippine Society of Digestive Endoscopy. SBML involved learning fine-tip control, structured upper endoscopy examination, and endoscopic therapies. Basic knowledge and interpretation of endoscopy findings were learned simultaneously. Interestingly, the first 5 wk of the program were conducted remotely using virtual coaching. Trainees used simulators and recorded their own performance, number of attempts, and completion time for each attempt, and then supervisors provided feedback based on these attempts. During the last week, trainees underwent in-person endoscopic therapy training after having passed the standard for fine-tip control and structured upper endoscopy examination. This study found that the adoption rates for basic endoscopic techniques such as image documentation and biopsy were 93% and 100%, respectively, after 2 mo of training. Meanwhile, the adoption rates of endoscopic therapies such as clipping, band ligation, and injection were more variable (7%-79%)[63]. Soetikno *et al*[64] also conducted an SBML course in GI bleeding endoscopic therapy and found that SBML quickly disseminated technical knowledge and skills. They proposed SBML as an additional method for teaching before trainees performed the procedure on patients.

PLANNING AND MANAGEMENT OF SIMULATION-BASED MASTERY LEARNING IN GI ENDOSCOPY

As stated above, the SBML program requires a developed and tested curriculum to ensure that all trainees can achieve competence in endoscopy. Kern *et al*[65] constructed a six-step approach to build an SBML curriculum. The steps are problem identification and general need assessment, specific need assessment, targets and objectives, educational strategies, implementation, and evaluation and feedback. Hospitals and medical institutions should delegate a specific team to plan the SBML curriculum. After planning, a pilot study should be conducted to evaluate satisfaction of trainees with the program and patient outcomes. Once SBML has been implemented, continuous monitoring and evaluation should be performed to maintain the quality of the program[37].

SBML begins with an initial assessment of the knowledge and abilities of trainees. After training, students will be tested again, and training will continue until they meet the minimum passing standards. Once trainees meet the minimum passing standards, they can advance to the next stage of training (Figure 1). Periodic examinations will be conducted along with planned practices to ensure that expected competencies are maintained[37]. Some training centers might provide materials for self learning before the simulation starts to improve the initial knowledge of trainees. A study by Cheung *et al*[66] showed that preparation before SBML is substantial to improve the effectiveness of SBML. They found that web-based observational practice is superior to reading materials alone, as it increases learner engagement with instructional materials.

Learning targets should be determined from the beginning of the SBML program and arranged according to the SMART acronym: specific, measurable, attainable, relevant, and time-bound[59,60]. Trainees, trainers, and supervisors have to understand learning targets before starting the program. This understanding is beneficial because trainees can focus their learning on the important and necessary skills, and trainers and supervisors can provide structured feedback. Feedback is important in SBML and should be delivered in a specific manner: with only one or two important points at a time and preferably immediately after the procedure or simulation to be properly understood by trainees[67,68]. Feedback should also be constructive and not vague, allowing trainees to self-reflect and come up with potential solutions[31].



DOI: 10.4253/wjge.v14.i9.512

Figure 1 Stages in simulation-based mastery learning. Simulation-based mastery learning begins with a pretest to assess trainees' initial knowledge and abilities. Subsequently, trainees will undergo simulation based-training with formative assessment to direct their training. Lastly, trainees will be evaluated for competency through summative assessment (posttest) according to the minimum passing standards. Trainees who pass the test can advance to the next stage of training, while those who do not pass must receive additional training and practice until they meet the minimum passing standards.

In addition to training or lesson planning, an assessment plan is needed to create a training environment with maximum results. Assessment is vital to provide trainees with future directions for improvement and to ensure patient safety by issuing a passing standard[69]. At the beginning of mastery learning, a pretest has to be conducted to evaluate the initial knowledge of trainees[67]. Within the program, assessments are classified as formative or summative assessments. Formative assessment aims to direct training and support the self reflection and intrinsic motivation of trainees[70]. Meanwhile, summative assessment seeks to evaluate competency and practice eligibility[71]. There are five criteria to indicate the quality of an assessment: reliability, which shows the accuracy and reproducibility of a test: validity, which shows whether the test can be performed to evaluate the intended focused parameter; future impact of the assessment; acceptability by trainees and supervisors; and reasonable cost. Assessments can be conducted through written examinations, direct evaluations by clinical supervisors, direct observations, clinical simulations, or portfolios[69].

THE FUTURE OF SIMULATION-BASED MASTERY LEARNING IN GI ENDOSCOPY

It is reasonable and expected that novice endoscopists do not perform endoscopic procedures on human patients unless they have shown satisfactory skills on a simulator. Endoscopy training should move from the traditional apprenticeship model to objective competency-based mastery learning, integrating simulators, deliberate practice, and prompt feedback from supervisors. The SBML curriculum is acknowledged as a method to boost the efficiency and efficacy of endoscopy training through repetitive practice and expert feedback, which allow trainees to learn the basic structure of endoscopic techniques. One of the limitations of the traditional apprenticeship model is the reduced time for questions, feedback, and adequate skill assessment during a procedure on an actual patient, which results in self learning; thus, not all trainees might develop a proper form and technique. Incorporating simulators can reduce this limitation of the conventional apprenticeship model by allowing trainees to practice basic endoscopic maneuvers repeatedly, as each trainee has a different absorption rate. In fact, acquiring proper techniques is essential for trainees, as they can progress to the next stage of training which is more complex. Simulators also limit the possibility of patient discomfort and injury, thereby allowing trainees to improve their skills. Additionally, the standardization of simulator-based instruction methods is essential to maximize the positive impact of the training method[8]. The integration of simulator in endoscopy training should be within a structured curriculum that combines constructive feedback and complementary knowledge[72]. A previous randomized trial compared the outcome of structured comprehensive curriculum to progressive learning-based curriculum, and revealed that those who received SBT that progressed in complexity and difficulty had superior technical and communication skills and global performance in the simulated setting[73].

A proper SBML curriculum for GI endoscopy should subsequently consist of cognitive, technical, and integrative skill training. The coronavirus disease 2019 pandemic has accelerated the acceptance of online video/web-based learning, video mentoring, and video proctoring. Web-based learning in the form of online modules is now expected for cognitive skill training, which allows trainees to review learning modules at their own pace and to avoid cognitive overload due to a stressful environment[59]. The main drawbacks of simulation-based learning are model realism and less real-world experience for new endoscopists. Hence, hybrid learning that combines simulator-based and one-on-one training is ideal for building the learning curves of trainees and identifying their deficiencies[74]. Improved performance in simulator training has been shown to translate into the clinical area[60].

CONCLUSION

The traditional apprenticeship model in GI endoscopy training must be revised to ensure competency and practical eligibility of novice endoscopists. By moving the focus from a case volume-based to a competency-based training, mastery learning can help lower the variability between skills of trainees and provide optimal results. Previous experiences with the SBML program in endoscopy training showed promising results and positioned that method as an additional course to be incorporated before the apprenticeship is started and also as a complementary course to one-on-one training. The use of a simulator in SBML can help trainees become acquainted with the endoscopic equipment, settings, and situations that might arise during their direct practice on patients. The SBML program should be planned and managed by a specific team and conducted within a developed and tested curriculum.

FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

Endoscopic ultrasound elastography for malignant pancreatic masses and associated lymph nodes: Critical evaluation of strain ratio cutoff value

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Abstract

BACKGROUND

Endoscopic ultrasound (EUS) can detect small lesions throughout the digestive tract; however, it remains challenging to accurately identify malignancies with this approach. EUS elastography measures tissue hardness, by which malignant and nonmalignant pancreatic masses (PMs) and lymph nodes (LNs) can be differentiated. However, there is currently little information regarding the strain ratio (SR) cutoff in Hispanic populations.

AIM

To determine the diagnostic accuracy of EUS elastography for PMs and LNs with an SR cutoff value in Hispanics.

METHODS

A retrospective study of patients who underwent EUS elastography for PMs between December 2013 and December 2014. A qualitative (analysis of color maps) and quantitative (SR) analysis of PMs and their associated LNs was performed. The accuracy of EUS elastography in identifying malignant PMs and LNs and cutoff value for SR were analyzed. A PM and/or its associated LNs were considered malignant based on histopathological findings from fine-needle aspiration biopsy samples.

RESULTS

A sample of 121 patients was included, 45.4% of whom were female. 69 (57.0%) PMs were histologically malignant, with a median SR of 50.4 *vs* 33.0 for malignant *vs* nonmalignant masses (P < 0.001). EUS evaluation identified associated LNs in 43/121 patients (35.5%), in whom 22/43 (51.2%) patients had histologically confirmed malignant diagnosis, with a median SR of 30 *vs* 40 for malignant *vs* nonmalignant LNs (P = 0.7182). In detecting malignancy in PMs, an SR cutoff value of > 21.5 yielded a sensitivity of 94.2%, while a cutoff value of > 121 yielded a specificity of 96.2.2%. There were significant differences in the Giovannini scores, a previously established elastic score system, between the patients grouped by their final histology results (P < 0.001). For LNs, SR cutoff values of > 14.0 and > 155 yielded a sensitivity of 90.9% and a specificity of 95.2%, respectively, in detecting malignancy.

CONCLUSION

EUS elastography is a helpful technique for the diagnosis of solid PMs and their associated LNs. The proposed SR cutoff values have a high sensitivity and specificity for the detection of malignancy.

Key Words: Ultrasound; Elastography; Pancreas; Lymph nodes; Neoplasm

Core Tip: This single-center retrospective study aimed to determine the diagnostic accuracy of endoscopic ultrasound (EUS) elastography in the diagnosis of pancreatic masses (PMs) and associated lymph nodes (LNs) with a defined strain ratio (SR) cutoff value in a Hispanic population. In determining if PMs were malignant, an SR cutoff value > 21.5 had a sensitivity of 94.2%, while a cutoff value > 121 had a specificity of 96.2.2%. For diagnosing LNs, an SR cutoff value > 14.0 had a sensitivity of 90.9%, while a cutoff value > 155 had a specificity of 95.2% for malignancy. The proposed SR cutoff values have high sensitivity and specificity for malignancy detection during EUS elastography.

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INTRODUCTION

Pancreatic masses (PMs) include neoplastic and nonneoplastic lesions (*i.e.*, anatomical variants, inflammatory lesions). One of the essential tasks during the assessment of PMs is identifying their benign or malignant nature. Along with the identification of malignant lesions, the presence of involved lymph nodes (LNs) is a prognostic factor of the disease. To date, one of the most sensitive methods for detecting PMs is endoscopic ultrasound (EUS), which allows for the visualization of small lesions throughout the digestive tract; however, EUS has a limited capacity in accurately determining the malignant or nonmalignant nature of a lesion. In addition, EUS-guided fine-needle aspiration (EUS-FNA) provides a histological diagnosis for lesions suspicious of malignancy; nevertheless, this invasive technique has a false-negative rate of 25%[1].

These shortcomings have been addressed with EUS elastography, an additional imaging technique used to determine tissue hardness. Malignant tissue is often more rigid than the normal surrounding tissue; thus, EUS elastography can differentiate between malignant and nonmalignant lesions. As a result, this technique has been applied in the diagnostic workup of PMs and their associated LNs[2-4]. EUS elastography is considered an accurate imaging technique for characterizing and detecting pancreatic lesions[2].

EUS elastography can be used to evaluate PMs and their associated LNs through qualitative and quantitative analyses; the former involves the analysis of color maps, while the latter is achieved by assessing the strain ratio (SR). However, previous studies, such as the one published by Altonbary *et al* [4], have reported differences in the SR cutoff value and the optimal internal sensitivity and specificity, suggesting a potential limitation of this technique[3,4]. The accuracy of this technique in differentiating malignant from nonmalignant lesions has only been assessed for masses consisting of solid tissue. The suitability of EUS elastography for solid-cystic lesions, which comprise an important percentage of

pancreatic tumoral lesions, has not been reported.

Based on the above, through this retrospective study, we aim to determine the diagnostic accuracy of EUS elastography for diagnosing malignant PMs and LNs in a Hispanic cohort and define the SR cutoff values in this population, comparing the results with those obtained through FNA biopsy.

MATERIALS AND METHODS

Study design

This was an observational, analytic, retrospective, case-control study performed at the Instituto Ecuatoriano de Enfermedades Digestivas (IECED, Guayaquil, Ecuador) from December 2013 to December 2014. Consecutive Hispanic patients (≥ 18 years old) were referred for the evaluation of suspected PMs using EUS following computed tomography (CT) or magnetic resonance imaging (MRI). Patients with incomplete clinical records were excluded. The patients were allocated into two groups (malignant or nonmalignant) according to the histological findings of biopsy samples and results from a 6-mo clinical follow-up (*i.e.*, laboratory tests, imaging, and surgical findings). All participants or their legal guardians gave written informed consent before the procedure. The Institutional Review Board approved the use and management of the corresponding data, and the study was conducted in accordance with the Declaration of Helsinki.

EUS elastography

All procedures were performed by two expert endoscopists (CRM and RV), who perform ≥ 300 EUS procedures *per* year. The patients were examined under general anesthesia using a 3.8 mm working-channel linear-array echoendoscope (EG3870UTK, Pentax Medical, Pentax, Hamburg, Germany) attached to a Hitachi AVIUS Ultrasound Console (Avius Hitachi, Tokyo, Japan).

First, PMs or any associated LNs were examined under conventional B-mode scanning. Then, EUS elastography of the region of interest was performed using the ultrasound console. Tissue hardness was measured qualitatively and quantitatively in all regions of interest *via* EUS color maps and the SR, respectively. Subsequently, EUS-guided FNA was performed using a 22-gauge needle (Expect®, Boston Scientific, Marlborough, MA). A pathologist blinded to the EUS elastography results performed the histological analysis.

Scoring system

Two expert endoscopists (CRM and RV) performed the qualitative assessed by classifying the elastography images using the elastic score, as reported by Giovannini[3]. Giovannini elastic scores of 1 and 2 correspond to large green areas of soft and nonmalignant tissue; a score of 3 corresponds to a mainly blue area, considered a small adenocarcinoma; scores of 4 and 5 correspond to blue areas of hard and malignant tissue. For practical purposes, scores of 1 and 2 were considered nonmalignant lesions, whereas scores of 3, 4, and 5 were considered malignant lesions. Conventional EUS B-mode characteristics, such as size, shape, density, and ability to determine the border of suspicious lesions, were also recorded as part of the qualitative analysis. According to these factors, lesions with a size greater than 1 cm, irregular shape, anechoic density, or undefined borders were considered malignant[3-6].

The quantitative diagnosis was performed by calculating the *semiquantitative proportion* of tissue elasticity by measuring the SR of the region of interest. According to the method described by Iglesias-Garcia *et al*[6], at least three elasticity measurements for the mass lesion (A) and one for the surrounding area (B) were obtained. The corresponding SRs were then calculated by dividing B by each of the A values, and their mean was calculated[7]

Data collection

Baseline data were extracted from medical records. The location, size, diameter, and color pattern of PMs and their associated LNs on EUS elastography, SR, and histological diagnosis were thoroughly described. Malignancy in solid and solid-cystic PMs was defined following the Fukuoka Consensus Guidelines, as detailed in Table 1[5].

Statistical analysis

Technical considerations: All statistical analyses were performed by an institutional GI attending and biostatistician (MPT) with 8 years of experience, sing R v4.0 (R Foundation for Statistical Computing; Vienna, Austria). A P value < 0.05 was considered statistically significant.

Sample size: The sample size was estimated considering a 100% specificity for an SR > 6.04 on EUS elastography in predicting malignancy in solid PMs, with a corresponding disease prevalence of 67.4% [5], δ = 10%, and α- and β-errors of 5% and 20%, respectively. Using these parameters, a sample size of twenty-four cases and eleven controls was estimated, with 80% statistical power. To respect the central limit theorem (in which thirty observations are necessary to reach a Gaussian distribution), we aimed to analyze no fewer than thirty patients with malignant PMs during the study period.

Table 1 Classification of pancreatic lesions

	Malignant	Nonmalignant
Solid	Adenocarcinoma	Acute pancreatitis
	Lymphoma	Chronic pancreatitis
	PNETs	Adenoma
	Pancreatoblastoma	Insulinoma
	Metastatic cancer	
Solid-Cystic	Mucinous cystadenoma[1]	Serous cystadenoma
	Serous cystadenocarcinoma	
	Mucinous cystadenocarcinoma	
	IPMN[1]	

[1]Considered malignant if the Fukuoka criteria are met.

PNET: Pancreatic neuroendocrine tumor; IPMN: Intraductal papillary mucinous neoplasm.

Comparisons of baseline data, EUS, and EUS elastography diagnostic outcomes: Quantitative variables are described as the mean (standard deviation) or median (minimum-maximum range) according to their statistical distribution (Kolmogorov-Smirnov test). Qualitative variables are described as frequency (%). The potential differences in baseline data (*i.e.*, age, sex, PM location) and EUS elastography diagnostic outcomes between malignant and nonmalignant PMs and LNs were confirmed with statistical hypothesis testing and illustrated with a boxplot, when necessary. Associations of PM and LN SR with diameter were demonstrated through Spearman's rank correlation (rho).

EUS and EUS elastography qualitative analysis: The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of a Giovannini elastic score of 3 to 5 (cyan and dark blue) in predicting malignancy in PMs and their associated LNs were estimated. In the case of PMs, the subgroup analysis considered only solid PMs (excluding solid-cystic PMs). In the case of associated LNs, the sensitivity, specificity, PPV, NPV, and accuracy of conventional B-mode EUS criteria in predicting malignancy were also determined.

EUS elastography quantitative analysis: The sensitivity, specificity, PPV, NPV, and accuracy of SR measurements in predicting malignancy in PMs and their associated LNs were estimated. Subgroup analysis was also performed for only solid PMs (excluding solid-cystic PMs). In each situation, two internally derived SR cutoff values, one yielding the optimal sensitivity (and accuracy) and the other the optimal specificity, were calculated from the study data. We also calculated the corresponding areas under the receiver operating characteristic curve (AUROCs), in which AUROCs of 0.5 suggested a prediction of malignancy equivalent to chance, with values of 0.7 to 0.8 considered acceptable, 0.8 to 0.9 considered excellent, and more than 0.9 considered outstanding discriminability[6]. The corresponding ROC curves were also generated and compared using the *roc.test* function of the *pROC* (v1.16.2; Robin X, 2020) package when necessary.

RESULTS

A sample of 121 patients with previous CT or MRI scans for PMs underwent EUS evaluation and were enrolled in the study. In this cohort, 55/121 (45.5%) were female, and the median age was 67 years (13–99). There was a histologically confirmed diagnosis of malignancy in 69/121 (57%) patients who were allocated to the malignant group; the remaining patients were placed in the nonmalignant group. Additionally, 43/121 (35.5%) patients had associated LNs surrounding the gastrointestinal tract. The baseline data and EUS elastography diagnostic outcomes of the cohort are summarized in Table 2.

We compared both PM groups in terms of the variables obtained from the EUS elasticity qualitative and quantitative analyses. Regarding the qualitative outcomes, there were significant differences in the Giovannini scores between the patients grouped by their final histology results ($P < 0.001$). For the quantitative outcomes, there was a significant difference in the median SR between patients with malignant (50.4, range 7.8–22.5) and nonmalignant PMs (33.0, range 2.6–321.0) ($P < 0.001$). In the solid PM subgroup, the median SR values were 51.0 (7.8–225.0) and 21.9 (2.6–321.0), respectively (Figure 1). A proportionally significant association was demonstrated between a higher PM SR and a larger PM diameter (rho = 0.251, 95%CI: 0–0.481; $P = 0.05$).

Table 2 Baseline data and endoscopic ultrasound elastography diagnostic outcomes of pancreatic masses

	Malignancy (*n* = 69)	Nonmalignancy (*n* = 52)	*P* value
Age (yr), median (range)	67 (13–93)	68 (20–99)	0.8907[a]
Sex (female), *n* (%)	36 (52.2)	19 (36.5)	0.1271[b]
PM location, *n* (%)			0.6891[b]
Head	50 (72.5)	35 (67.3)	
Neck	3 (4.3)	4 (7.7)	
Body	13 (18.8)	12 (23.1)	
Tail	3 (4.3)	1 (1.9)	
PM diameter (mm), median (range)	37.0 (7.4–70.0)	30 (10.0–60.0)	0.0616[a]
Giovannini elastic score, *n* (%)			< 0.001[b]
Green (score 1 to 2)	-	11 (21.2)	
Cyan (score 3)	5 (7.2)	11 (21.2)	
Dark blue (score 4 to 5)	64 (92.8)	30 (57.7)	
Strain ratio, median (range)	50.4 (7.8–225.0)	33.0 (2.6–321.0)	< 0.001[a]
Firmness/histopathology, *n* (%)			< 0.001[b]
Solid-cystic masses (*n* = 36)	26/69	10/52	< 0.001[b]
Serous cystadenoma	-	10 (19.2)	
Mucinous cystadenoma	5 (7.2)	-	
Mucinous cystadenocarcinoma	3 (4.3)	-	
IPMN	18 (26.1)	-	
Solid masses (*n* = 85)	43/69	42/52	< 0.001[b]
Normal	-	4 (7.7)	
Acute pancreatitis	-	10 (19.2)	
Chronic pancreatitis	-	26 (50.0)	
Adenoma	-	1 (1.9)	
Insulinoma	-	1 (1.9)	
Adenocarcinoma	33 (47.8)	-	
Lymphoma	3 (4.3)	-	
PNETs	6 (8.7)	-	
Pancreatoblastoma	1 (1.4)	-	

[a]Mann-Whitney U test.
[b]Pearson Chi-Quadrat Test.
IPMN: Intraductal papillary mucinous neoplasm; PNET: Pancreatic neuroendocrine tumor; PM: Pancreatic masses.

In detecting malignancies among all PMs, a Giovannini elastic score of 3 to 5 had a sensitivity, specificity, PPV, NPV, and accuracy of 100.0%, 21.2%, 62.7%, 100.0%, and 66.1%, respectively. For the subgroup of solid PMs, the corresponding sensitivity, specificity, PPV, NPV, and accuracy were 100%, 23.8%, 57.3%, 100%, and 62.4%, respectively (Table 3).

In the quantitative analysis, we found that optimal sensitivity and specificity values were obtained for SR cutoff values of 21.5 and 121.0, respectively, for both all PMs and solid PMs. The diagnostic accuracy parameters for both groups of PMs are shown in Table 3. Notably, in the overall PM analysis, the lower SR cutoff value (≥ 21.5) was associated with a higher sensitivity (94.2%) and NPV (84.0%), and the higher SR cutoff value (≥ 121.0) was associated with higher specificity (96.2%) and PPV (83.3%). A similar observation was made in the solid PM subgroup analysis; however, the SR cutoff value of ≥ 121.0 yielded higher accuracy in the subgroup analysis than in the overall PM analysis (54.1% *vs* 49.6%), while the SR cutoff of ≥ 21.5 yielded a lower accuracy (69.4% *vs* 71.1%). Additionally, the AUROC was slightly higher in the solid PM subgroup analysis (AUROC = 0.713) than in the overall PM analysis

Table 3 Qualitative and quantitative diagnostic accuracy of endoscopic ultrasound elastography for detecting malignant pancreatic masses: All lesions (*n* = 121) and only solid pancreatic masses (*n* = 85)

	EUS-elastography qualitative analysis		EUS-elastography quantitative analysis			
	All masses	Only solid pancreatic masses	All PMs		Only solid PMs	
			SR ≥ 21.5[1]	SR ≥ 121.0[2]	SR ≥ 21.5[1]	SR ≥ 121.0[2]
Sensitivity (%)	100.0	100.0	94.2	14.5	90.7	14.0
Specificity (%)	21.2	23.8	40.4	96.2	47.6	95.4
PPV (%)	62.7	57.3	67.7	83.3	63.9	70.0
NPV (%)	100.0	100.0	84.0	45.9	83.3	52.0
Accuracy (%)	66.1	62.4	71.1	49.6	69.4	54.1

[1]Internally derived optimal strain ratio (SR) cutoff for sensitivity (and accuracy).
[2]Internally derived optimal SR cutoff for specificity.
EUS: Endoscopic ultrasound; SR: Strain ratio; PPV: Positive predictive value; NPV: Negative predictive value; PM: Pancreatic masses.

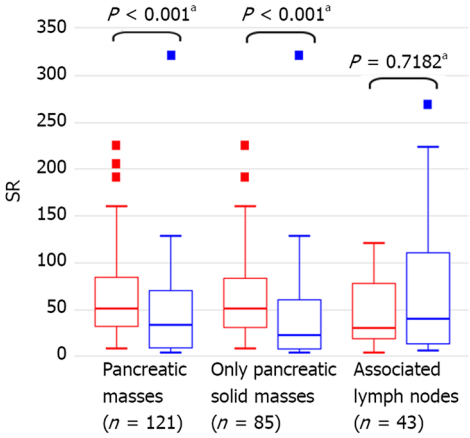

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Figure 1 Distribution of strain ratio values among malignant (red) and nonmalignant (blue) pancreatic masses and their associated lymph nodes. [a]Mann-Whitney U test. SR: Strain ratio.

(AUROC = 0.685) (*P* = 0.7073) (Figure 2A and B).

Among the 43 patients with associated LNs, the median age was 67.5 (39–95) years, and 14/43 (32.6%) were female. Histology confirmed malignancy in 22/43 (51.2%) patients, who were subsequently placed in the malignant group. There were no significant differences between the malignant and nonmalignant LN groups in LN location, diameter, EUS characteristics, Giovannini elastic score, or SR (Table 4). Specifically, the average SR was 30.0 (3.0–120.0) for malignant LNs and 40.0 (5.0–269.0) for nonmalignant LNs (*P* = 0.7182) (Figure 1). There was no association between LN SR and diameter (rho = -0.017, 95%CI: -0.503–0.421; *P* = 0.937).

Qualitative EUS elastography analysis yielded a sensitivity, specificity, PPV, NPV, and accuracy of 68.1%, 38.1%, 53.6%, 53.3%, and 53.5%, respectively; these values were lower than those obtained using the structural characteristics detected *via* conventional B-mode scanning (Table 5). For the PMs, we obtained two SR cutoff values by identifying the values that yielded optimal sensitivity and specificity. Specifically, an SR cutoff value of 14.0 yielded a sensitivity, specificity, PPV, NPV and accuracy of 90.0%, 28.6%, 51.4%, 75.0% and 60.4, respectively; the corresponding values for an SR cutoff value of 155.0 were 4.5%, 95.2%, 50.0%, 48.8% and 48.8% (Table 5). The use of SR for diagnosing malignancy yielded an AUROC of 0.417 (Figure 2C).

DISCUSSION

In the present study, we found that qualitative EUS elastography analysis was highly sensitive for solid PMs. Moreover, in the quantitative assessment, an SR cutoff value of ≥ 21.5 had a 90% sensitivity for

Table 4 Baseline data, endoscopic ultrasound, and endoscopic ultrasound elastography diagnostic outcomes of the associated lymph nodes

	Malignancy (*n* = 22)	Nonmalignancy (*n* = 21)	*P* value
Age (yr), median (range)	76 (57–95)	65 (39–85)	0.2037[a]
Sex (female), *n* (%)	8 (36.4)	6 (28.6)	0.5860[b]
LN location, *n* (%)			0.4250[b]
Esophagus	13 (59.1)	15 (71.4)	
Stomach	2 (9.1)	1 (4.8)	
Liver	1 (4.5)	-	
Pancreas	5 (22.7)	5 (23.8)	
Kidney	1 (4.5)	-	
LN diameter, median (range)	20.0 (4.0–50.0)	15.5 (7.0–21.6)	0.2662[a]
EUS-LN characteristics, *n* (%)			
Irregular shape	11 (50.0)	10 (47.6)	0.8760[b]
Undefined border	13 (59.1)	8 (38.1)	0.2730[b]
Anechoic density	7 (31.8)	3 (14.3)	0.1740[b]
Giovannini elastic score, *n* (%)			0.7970[b]
Green (score 1 to 2)	1 (4.5)	2 (9.5)	
Cyan (score 3)	6 (27.3)	6 (28.6)	
Dark blue (score 4 to 5)	15 (68.2)	13 (61.9)	
Strain ratio, median (range)	30.0 (3.0–120.0)	40.0 (5.0–269.0)	0.7182[a]
Histopathology, *n* (%)			< 0.001[b]
Acute lymphadenitis	-	10 (47.6)	
Chronic lymphadenitis	-	11 (52.4)	
Lymphoma	2 (9.1)	-	
Metastasis	20 (90.9)	-	

[a]Mann-Whitney U test.
[b]Pearson Chi-Quadrat Test.
EUS: Endoscopic ultrasound; LN: Lymph node.

defining malignancy in solid PMs (Figure 3). In contrast, a cutoff value of ≥ 121.0 had a 95% specificity for malignant PMs. For the evaluation of associated LNs, an SR of ≥ 14.0 had a 91% sensitivity, whereas an SR of ≥ 155.0 had a 95% specificity.

Various studies have shown the ability of EUS to distinguish between malignant and nonmalignant lesions. Itokawa *et al*[8] proposed that a Giovannini elastic score of 5 during EUS elastography evaluation is a characteristic of pancreatic malignancy[8,9], with 98.6% of patients having a score of five and a confirmed pancreatic malignancy. However, our study found that 91.4% of patients with malignant PMs had a score of 4 to 5.

The qualitative elastic score had a high sensitivity of 100.0% in our study for solid and solid-cystic PMs. On the other hand, Itokawa *et al*[8] found that a considerable number of nonmalignant cases scored 5, decreasing the specificity of the elastic score to 64.3%[2]. Our study found a specificity of 21.15% for solid and solid-cystic PMs and 23.81% for solid masses alone. No malignant pancreatic lesions had an elastic score of 1 or 2 following Giovannini's classification. According to the qualitative analysis, our cases reported high sensitivity and NPV.

Iglesias-Garcia *et al*[6], in a prospective study of 86 patients, described one of the highest diagnostic accuracy values based on qualitative and quantitative EUS elastography analysis. For the qualitative measurements, the sensitivity, specificity, PPV, NPV, and overall accuracy were 100%, 71%, 87%, 100%, and 90%, respectively. For the quantitative values, a lower SR cutoff value of > 6.0 had a sensitivity, specificity, PPV, NPV, and overall accuracy of 100%, 92%, 96%, 100%, and 97%, respectively[6].

Table 5 Diagnostic accuracy of conventional B-mode endoscopic ultrasound and qualitative and quantitative endoscopic ultrasound elastography analysis for malignancy in the associated lymph nodes (*n* = 43)

	Conventional B-mode EUS				EUS-elastography qualitative analysis	EUS-elastography quantitative analysis	
	Size	Shape	Border	Density		SR ≥ 14.0[1]	SR ≥ 155.0[2]
Sensitivity (%)	59.1	50.0	59.1	31.8	68.1	90.9	4.5
Specificity (%)	42.9	52.4	61.9	85.7	38.1	28.6	95.2
PPV (%)	52.0	52.4	61.9	70.0	53.6	51.4	50.0
NPV (%)	50.0	50.0	59.1	54.6	53.3	75.0	48.8
Accuracy (%)	51.2	51.2	60.5	58.1	53.5	60.4	48.8

[1]Internally derived optimal strain ratio cutoff for sensitivity (and accuracy).
[2]Internally derived optimal cutoff for specificity.
EUS: Endoscopic ultrasound; SR: Strain ratio; PPV: Positive predictive value; NPV: Negative predictive value.

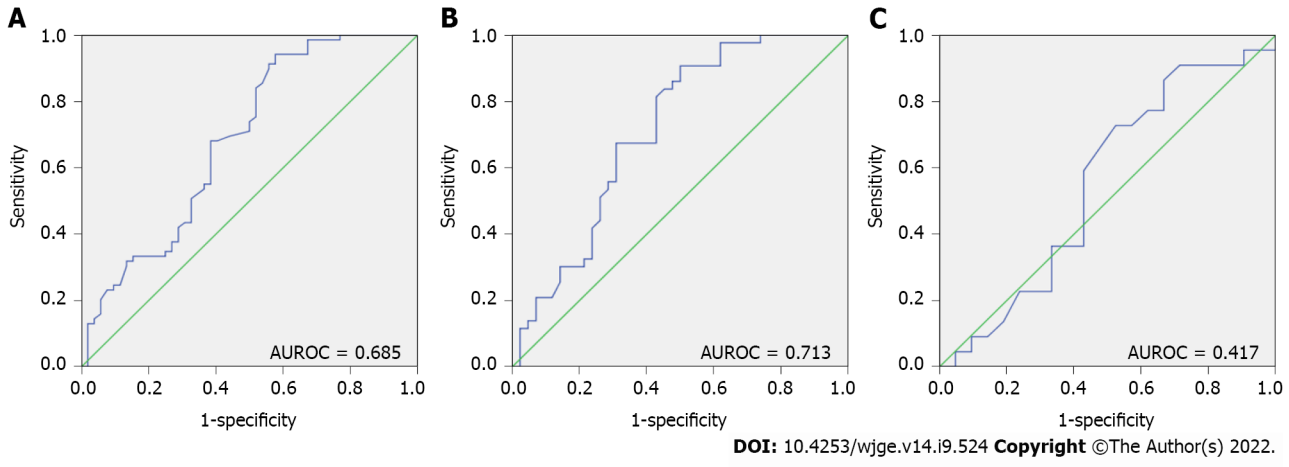

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Figure 2 Areas under the receiver operating characteristic curve. A: Areas under the receiver operating characteristic curve (AUROC) of the strain ratio in the detection of malignancy in pancreatic masses [AUROC = 0.685 (0.586–0.783)], B: AUROC of the strain ratio in the detection of malignancy in only solid pancreatic masses [AUROC = 0.713 (0.602–0.825)]; C: AUROC of the strain ratio in the detection of malignancy in associated lymph nodes [AUROC = 0.417 (0.076–0.757)]. There was no significant difference between AUROC–A and AUROC–B (*P* = 0.7073). AUROC: Areas under the receiver operating characteristic curve.

Dawwas *et al*[10] obtained a higher diagnostic accuracy for EUS elastography using an SR cutoff value of 4.65 to achieve a 100% sensitivity and a cutoff value of 59.25 to achieve a 100% specificity. Okasha *et al*[11] concluded that the best SR cutoff level was 7.8, which gave a sensitivity of 92%, a specificity of 77%, a PPV of 91%, an NPV of 80%, and an accuracy of 88%[11]. Our study achieved a higher sensitivity using a lower cutoff value. Actors such as tissue inflammation, fibrosis, necrosis, advanced age, or ethnicity may affect the hardness of tissue, explaining the difference in the cutoff values proposed in the literature[12-14]. Moreover, the size of the region of interest and tissue compression level could affect the quantitative evaluation of EUS elastography.

Additionally, a study published by Kongkam *et al*[15] showed that a cutoff SR level of 3.17 along with EUS-FNA provided a sensitivity, specificity, PPV, NPV and accuracy of 95.2%, 71.4%, 90.9%, 83.3%, and 89.3%, respectively, compared to the 90%, 100%, 100% 80% and 92.8% of EUS elastography alone. Based on these results, the authors raised the possibility of a future combination of both techniques for evaluating PMs[15].

Paterson *et al*[12] focused their research on the utility of quantitative EUS elastography analysis for defining malignancy in the LNs related to esophageal and gastric cancer and compared this approach to an analysis using conventional EUS LN features. Compared to our results, they found a lower diagnostic accuracy for conventional EUS but a higher diagnostic accuracy for EUS elastography[12].

The present study has several limitations, including its retrospective design and single-center nature, leading to a limited number of operators. A few patients from the malignant case group underwent surgery, limiting the histological description of this research. The nonmalignant control group was defined as patients with nonmalignant masses instead of a healthy population. However, this study has

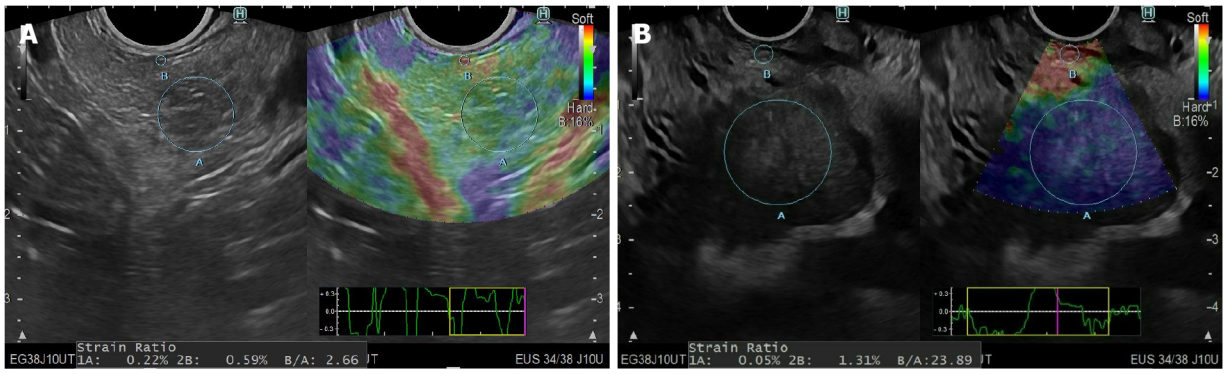

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Figure 3 Quantitative and qualitative endoscopic ultrasound elastography assessment. A: Case No. 84: A 26-year-old women with a pancreatic mass. A plain B-mode image (left) and a color-code strain image (right) are shown, strain ratio (SR) = 2.66, Giovannini elastic score of 2 (green). Biopsy confirmed chronic pancreatitis; B: Case No. 73: A 46-year-old man with a pancreatic mass. A plain B-mode image (left) and a color-coded strain image (right) are shown, SR = 23.8, Giovannini elastic score of 4 (dark blue). Biopsy confirmed pancreatic adenocarcinoma.

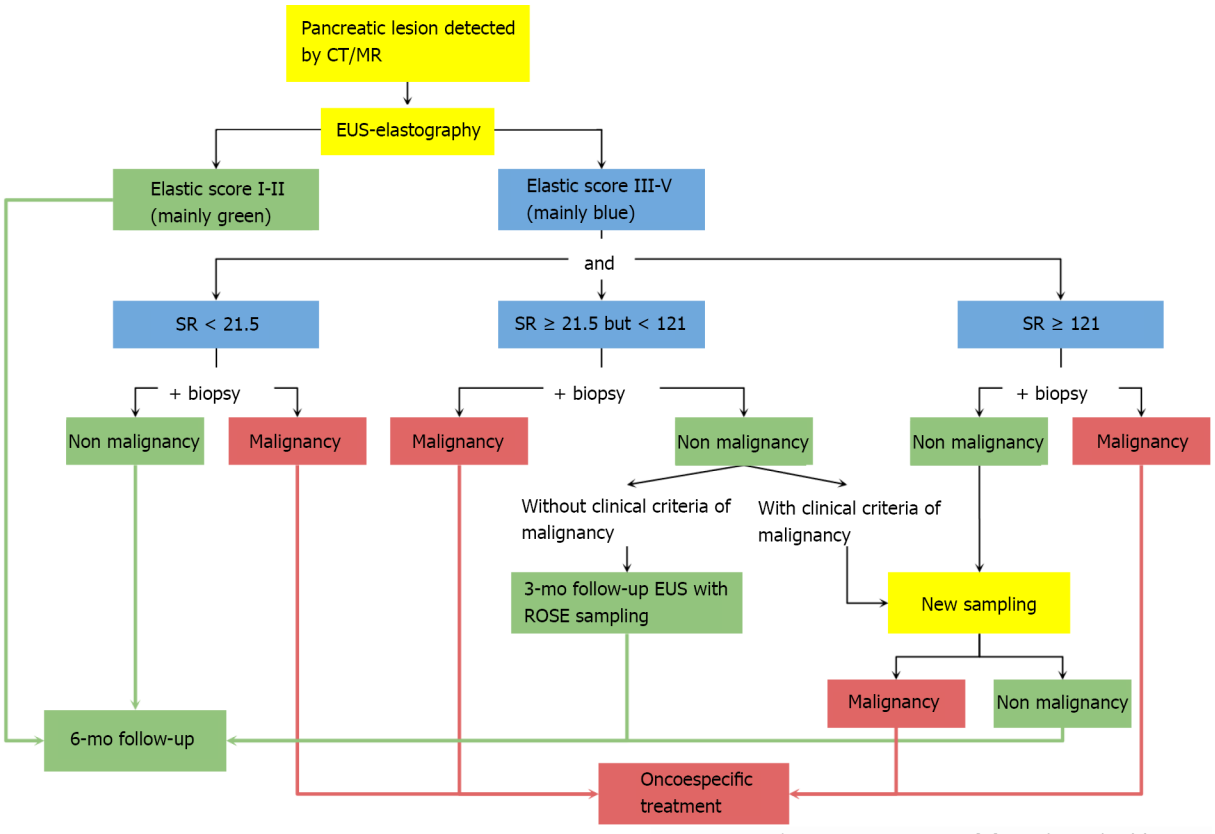

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Figure 4 Proposed algorithm for the workup of pancreatic masses. SR: Strain ratio; EUS: Endoscopic ultrasound; CT: Computed tomography; MR: Magnetic resonance.

the advantage of using the qualitative elastic score proposed by Giovannini[3]. For the interpretation of PMs and their associated LNs, instead of the 4-score by Furukawa *et al*[16], and may be one of the first studies to evaluate the utility of EUS elastography in Hispanic patients. Future research on this topic will be designed as diagnostic trials, considering the Giovannini score for PMs and associated LN descriptions.

Finally, hard PMs are not necessarily malignant all the time, whereas soft lesions are not necessarily nonmalignant[2,17]. Therefore, a validated cutoff value for defining malignancy in PMs and their associated LNs is imperative for obtaining an appropriate diagnosis and providing management guidance. Based on our findings, we recommend an SR cutoff values of > 121.0 and > 155.0 as criteria for supporting the need for FNA sampling of pancreatic lesions or their associated LNs, respectively. In

patients with SR values ranging from 21.5-121.0 and 14.0-155.0, sampling should be indicated if there is a high clinical suspicion of malignancy. Figure 4 shows a proposed clinical algorithm using EUS elastography evaluations. We recommend starting with a qualitative measurement. For those with a low risk of malignancy (elastic score I-II), a 6-mo follow-up is necessary. However, for those with an elastic score between 3 and 5, a quantitative evaluation is required to define the SR measurement and determine the necessity of FNA and whether a malignancy is suspected.

CONCLUSION

We found that EUS combined with qualitative and quantitative elastography analysis *via* SR is a helpful resource when assessing PMs and their associated LNs. This approach is more effective and convenient than limiting the evaluation to only conventional EUS-fine needle aspiration for the detection of malignancy. Although histological analysis is mandatory for a final diagnosis, elastography should be included in the diagnostic workup of PMs and their associated LNs. However, validating this recommendation through a prospective, multi-center, controlled trial is preferable.

ARTICLE HIGHLIGHTS

Research background

Endoscopic ultrasound (EUS) elastography can be a useful technique for the evaluation of pancreatic masses (PMs) and their associated lymph nodes (LNs) through qualitative (analysis of color maps) and quantitative (assessing the strain ratio).

Research motivation

The accuracy of this technique in differentiating malignant from nonmalignant lesions has only been assessed for masses consisting of solid tissue. For the evaluation of solid-cystic lesions, the suitability of EUS-elastography has not been reported.

Research objectives

To determine the diagnostic accuracy of EUS elastography and the strain ratio (SR) cutoff value for malignant PMs and LNs in a Hispanic cohort.

Research methods

A retrospective study of patients who underwent EUS elastography for PMs between December 2013 and December 2014. A qualitative and quantitative (SR) analysis of PMs and their associated LNs was performed. The accuracy of EUS elastography in identifying malignant PMs and LNs and cutoff value for SR were analyzed. A PM and/or its associated LNs were considered malignant based on histopathological findings from fine-needle aspiration biopsy samples.

Research results

Malignant PMs have a superior median SR compared to nonmalignant lesions (50.4 *vs* 33.0, respectively) ($P < 0.001$). When analyzing LNs, there was no statistical significance (SR 30.0 for PMs *vs* 40.0 for LNs) ($P = 0.7182$). An SR cutoff value > 21.5 in PMs yielded a 94.2% sensitivity. Meanwhile, an SR cutoff value > 14.0 yielded a 90.9% sensitivity.

Research conclusions

The proposed EUS elastography SR cutoff values have a high sensitivity and specificity for the detection of malignancy.

Research perspectives

Future research evaluating the utility of EUS elastography in Hispanic patients through a prospective, multi-center, controlled trial is necessary to validate our data.

FOOTNOTES

Author contributions: Puga-Tejada M and Oleas R performed design of the work, acquisition, analysis, and interpretation of data, drafting and critical revision of the manuscript for important intellectual content, and final approval of the version to be published; Del Valle R, Egas-Izquierdo M, Ospina J and Soria-Alcivar M contributed to the acquisition of data for the work, critical revision of the manuscript for important intellectual content, and final approval of the version to be published; Egas-Izquierdo M performed the final database consolidation and

encryption; Arevalo-Mora M and Baquerizo-Burgos J contributed to the acquisition and analysis of data, drafting the manuscript, and final approval of the version to be published; Pitanga-Lukashok H contributed to the conception and design of the work, critical revision of the manuscript for important intellectual content, and final approval of the version to be published; Robles-Medranda C contributed to the conception and design of the work, drafting and critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

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Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: Carlos Robles-Medranda is a key opinion leader and consultant for Pentax Medical, Boston Scientific, Steris, Medtronic, Motus, Microtech, G-Tech Medical Supply, CREO Medical, EndoSound, and Mdconsgroup. The other authors declare no conflicts of interest.

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STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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ORIGINAL ARTICLE

Retrospective Study

Screening for hilar biliary invasion in ampullary cancer patients

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Abstract

BACKGROUND

The treatment for ampullary cancer is pancreatoduodenectomy or local ampullectomy. However, effective methods for the preoperative investigation of hilar biliary invasion in ampullary cancer patients have not yet been identified.

AIM

To determine the necessity of and an appropriate method for investigating hilar biliary invasion of ampullary cancer.

METHODS

Among 43 ampullary cancer patients, 34 underwent endoscopic treatment (n = 9) or surgery (n = 25). The use of imaging findings (thickening and enhancement of the bile duct wall on contrast-enhanced computed tomography, irregularity on endoscopic retrograde cholangiography, thickening of the entire bile duct wall on intraductal ultrasonography (IDUS), and partial thickening of the bile duct wall on IDUS) and biliary biopsy results for diagnosing hilar biliary invasion of ampullary cancer was compared.

RESULTS

Hilar invasion was not observed in every patient. Among the patients who did not undergo biliary stent insertion, the combination of partial thickening of the bile duct wall on IDUS and biliary biopsy results showed the highest accuracy (100%) for diagnosing hilar biliary invasion. However, each imaging method and biliary biopsy yielded some false-positive results.

CONCLUSION
Although some false-positive results were obtained with each method, the combination of partial thickening of the bile duct wall on IDUS and biliary biopsy results was useful for diagnosing hilar biliary invasion of ampullary cancer. However, hilar invasion of ampullary cancer is rare; therefore, the investigation of hilar biliary invasion of ampullary cancer might be unnecessary.

Key Words: Ampullary cancer; Biliary biopsy; Contrast-enhanced CT; Hilar biliary invasion; Intraductal ultrasonography

Core Tip: The standard treatment for ampullary cancer is surgical resection. However, the necessity of and appropriate diagnostic method for assessing hilar invasion is unknown. In this study, the use of contrast-enhanced computed tomography, endoscopic retrograde cholangiography, intraductal ultrasonography (IDUS), and biliary biopsy for diagnosing hilar invasion of ampullary cancer was compared. Although false positives were observed for each method, the combination of partial thickening of the bile duct wall on IDUS and biliary biopsy results was efficient for accurately diagnosing hilar invasion of ampullary cancer. On the other hand, hilar invasion of ampullary cancer is rare; thus, hilar biliary investigation might be unnecessary.

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INTRODUCTION

The standard treatment for ampullary cancer is pancreatoduodenectomy. In addition, local surgical resection of the ampulla or endoscopic ampullectomy has been recently performed for ampullary cancer that does not invade the sphincter of Oddi[1-6]. To perform these treatments, an accurate assessment of the extent of biliary invasion is important. Although ampullary lesions show ductal invasion[7-9], hilar biliary invasion by ampullary lesions has not been reported. When a tumor advances to the hilar biliary duct, the extent of resection is modified accordingly.

The efficacy of contrast-enhanced computed tomography (CECT), endoscopic retrograde cholangiography (ERC), and intraductal ultrasonography (IDUS) for diagnosing the horizontal progression of bile duct cancer has been reported[10-15]. The diagnostic accuracy of CECT for lateral extension of hilar biliary cancer has been reported to be 71%-96%[13,14,16-23]. In addition, ERC following IDUS has been reported to be useful for diagnosing lateral extension of biliary ductal cancer[24-27]. The diagnostic accuracy of mapping biopsy for lateral extension of biliary ductal cancer has been reported to be 73.0%-89.0%[28-31]. However, whether these methods are effective for investigating hilar invasion in ampullary cancer patients is unknown. In this study, we aimed to reveal the best method for diagnosing hilar invasion in ampullary cancer patients.

MATERIALS AND METHODS

Study design and ethics

This retrospective study aimed to identify an appropriate screening method for hilar biliary invasion of ampullary cancer. This study was approved by the Institutional Review Board of Fukushima Medical University (approval number: 2453).

Patients

This study enrolled 43 ampullary cancer patients who were treated at Fukushima Medical University between September 2009 and December 2020. Among them, 34 patients underwent resection by endoscopic treatment (n = 9) or surgery (n = 25) (Table 1). Endoscopic ampullectomy was performed when invasion into the muscular layer or bile and pancreatic ducts was not observed by ERC or IDUS. It was not necessary to obtain informed consent from the patients because this study was retrospective in design and used previously anonymized clinical data. All the patients agreed to the clinical examination and treatment by providing written consent; in the case of participants under 18 years of age, consent was obtained from a parent and/or legal guardian. The details of the study can be found on the homepage of Fukushima Medical University. All methods were carried out in accordance with relevant guidelines and regulations.

Examination items

The final diagnosis of hilar biliary invasion was determined according to histological diagnosis and the nonexistence of local recurrence during follow-up for more than six months. When the horizontal margin of the resected specimen was negative, hilar invasion was considered negative.

Useful methods for diagnosing hilar invasion were investigated in 34 ampullary cancer patients who underwent endoscopic therapy or surgery. The assessed imaging findings of hilar biliary invasion were thickening and enhancement of the bile duct wall on CECT (Figure 1A), irregularity on ERC (Figure 1B), thickening of the entire bile duct wall on IDUS (Figure 1C), and partial thickening of the bile duct wall on IDUS (Figure 1D). The usefulness of hilar biliary biopsy was also considered. Thickening of the bile duct wall on IDUS was defined as a diameter of the bile duct wall greater than 2 mm.

All imaging findings were evaluated by more than two pancreaticobiliary disease specialists. Endoscopic retrograde cholangiopancreatography (ERCP) was performed as follows. With the patient in a prone position, a duodenoscope was inserted after sufficient sedation was achieved with midazolam. When the duodenoscope reached the Vater papilla, biliary cannulation was initiated. Tumor progression was evaluated by using ERC, IDUS, and hilar biliary biopsy. It is difficult to observe the whole circumference of the bile duct wall by EUS. Therefore, the evaluation of hilar invasion by EUS was not considered in this study.

JF260 V, JF240, and TJF240 duodenoscopes (Olympus, Tokyo, Japan) were used. An MTW ERCP tapered catheter (MTW Endoskopie, Wesel, Germany) and Tandem XL cannula (Boston Scientific Japan, Tokyo, Japan) were used as the ERC catheters. Endo Jaw FB231K (Olympus) or Radial Jaw™ 4 Biopsy Forceps (Boston Scientific Japan) were used for biliary biopsy.

Post-ERC pancreatitis (PEP) and adverse events were diagnosed according to Cotton's criteria[32]. PEP was defined as an elevated serum amylase level more than three times the normal upper limit with abdominal pain for more than 24 h after ERC. In addition, all PEP patients were confirmed to have peripancreatic inflammation by CECT. The severity of PEP was categorized as follows: mild: extended hospitalization for 2-3 d; moderate: extended hospitalization for 4-10 d; and severe: Extended hospitalization for more than 10 d, hemorrhagic pancreatitis, and pseudocysts that required intervention. The severity of bleeding was categorized as follows: Mild: Clinical evidence of bleeding, hemoglobin decrease < 3 g/dL, and no need for transfusion; moderate: Transfusion (4 units or less) and no angiographic intervention or surgery; and severe: Transfusion (5 units or more) or intervention (angiographic or surgical).

Statistical analyses

The imaging findings and biliary biopsy results were compared with respect to their ability to diagnose hilar invasion of ampullary cancer by Fisher's exact test. The Bonferroni method and Holm method were used to adjust for multiple comparisons. EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan) was used for statistical analysis. A P value < 0.05 was considered indicative of a significant difference.

RESULTS

Patient characteristics and treatment

The patient characteristics and treatment results are shown in Table 1. The mean age of the patients was 68.0 ± 11.1 years. There were 20 male patients and 14 female patients. The numbers of the different lesion stages were as follows: I: 16; II: 8; and III: 10. Disease stage was classified according to the Union for International Cancer Control classification 8th edition[33]. Four patients had already undergone biliary stent insertion in other hospitals. No histological hilar biliary invasion or local recurrence was observed in any patient.

Imaging findings and biopsy results of all patients

Among the methods explored for diagnosing hilar biliary invasion of ampullary cancer, hilar biliary

Table 1 Patient characteristics and treatment

Parameter	
Total patients, *n*	43
Unresectable or treated in other hospitals, *n*	9
Underwent resection, *n*	34
Age, yr (mean ± standard deviation)	68.0 ± 11.1
Sex, *n* (male/female)	20/14
UICC stage 8th edition, *n*	
I	16
II	8
III	10
Patients already having biliary stents, *n*	4
Treatment, *n*	
Endoscopic ampullectomy	9
Surgery	25
Hilar biliary invasion, *n*	0
Local recurrence, *n*	0

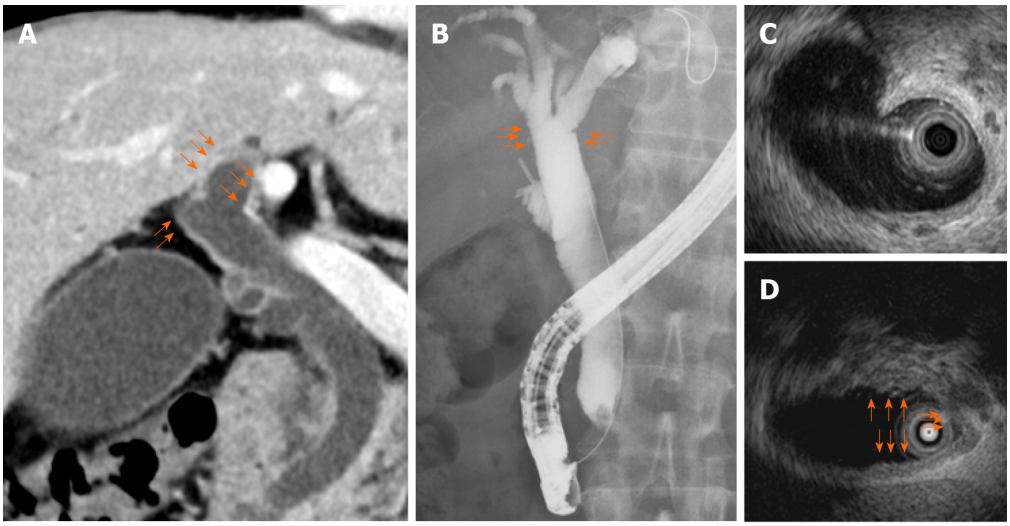

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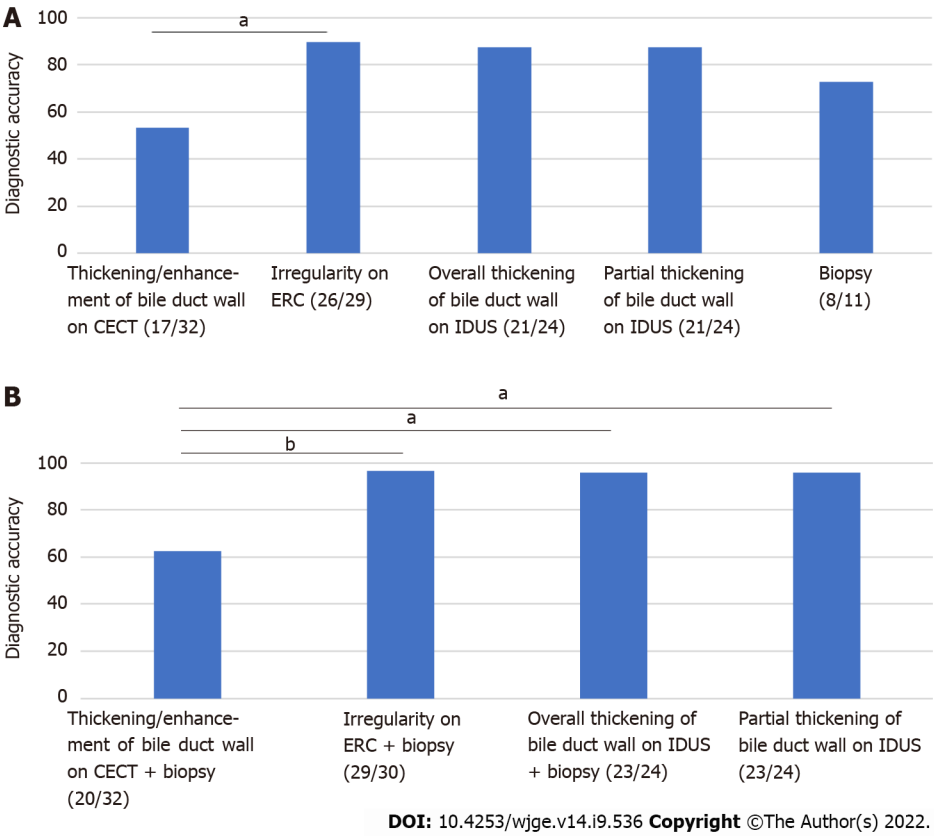
Figure 1 Imaging findings of the hilar biliary duct. A: Thickening and enhancement of the bile duct wall on contrast-enhanced computed tomography; B: Irregularity on endoscopic retrograde cholangiography; C: Thickening of the entire bile duct wall on intraductal ultrasonography (IDUS); D: Partial thickening of the bile duct wall on IDUS.

irregularity on ERC showed the highest diagnostic accuracy (thickening and enhancement of the bile duct wall on CECT: 53.1% (17/32); irregularity on ERC: 89.7% (26/29); thickening of the entire bile duct wall on IDUS: 87.5% (21/24); partial thickening of the bile duct wall on IDUS 87.5% (21/24), biliary biopsy results 72.7% (8/11), *P* value < 0.01) (Figure 2A). The diagnostic accuracy of irregularity on ERC for hilar invasion of ampullary cancer was significantly higher than that of thickening and enhancement of the bile duct wall on CECT (*P* value = 0.02).

Comparisons of the various combinations [imaging findings and biliary biopsy results) for diagnosing hilar biliary invasion revealed that the diagnostic accuracies of irregularity on ERC + biliary biopsy results (96.7% (29/30)], thickening of the entire bile duct wall on IDUS + biliary biopsy results [95.8% (23/24)], and partial thickening of the bile duct wall on IDUS + biliary biopsy results [95.8% (23/24)] were significantly higher than that of thickening and enhancement of the bile duct wall on CECT + biliary biopsy results [62.5% (20/32), *P* value < 0.01, = 0.02, and = 0.02, respectively] (Figure 2B).



DOI: 10.4253/wjge.v14.i9.536

Figure 2 Comparison of methods for diagnosing hilar biliary invasion of ampullary cancer in all patients. A: Irregularity on endoscopic retrograde endoscopic retrograde cholangiography (ERC) showed the highest diagnostic accuracy; B: Among the various combinations (imaging findings and biliary biopsy results) for diagnosing hilar biliary invasion, irregularity on ERC + biliary biopsy results showed the highest diagnostic accuracy. [a]*P* < 0.05, [b]*P* < 0.01. CECT: Contrast-enhanced computed tomography; ERC: Endoscopic retrograde cholangiography; IDUS: Intraductal ultrasonography.

Imaging findings and biopsy of patients who had not received biliary duct stents

Partial thickening of the bile duct wall on IDUS showed the highest diagnostic accuracy among the explored methods (thickening and enhancement of the bile duct wall on CECT: 57.1% (16/28); irregularity on ERC: 88.0% (22/25); thickening of the entire bile duct wall on IDUS: 84.2% (16/19); partial thickening of the bile duct wall on IDUS 89.5% (17/19); biliary biopsy: 66.7% (6/9); *P* value < 0.035 but no significant differences in pairwise comparisons) (Figure 3A).

Among the investigated combinations (imaging findings and biliary biopsy results) for diagnosing hilar biliary invasion of ampullary cancer, the combination of partial thickening of the bile duct on IDUS and biliary biopsy results showed the highest diagnostic accuracy (thickening and enhancement of the bile duct wall on CECT + hilar biliary biopsy results: 64.3% (18/28); irregularity on ERC + biliary biopsy results: 96.2% (25/26); thickening of the entire bile duct wall on IDUS + biliary biopsy results: 95.0% (19/20); partial thickening of the bile duct wall on IDUS + biliary biopsy results: 100% (20/20); *P* value < 0.01) (Figure 3B). The combination of irregularity on ERC and biliary biopsy results and the combination of partial thickening of the bile duct wall on IDUS and biliary biopsy results each had a significantly higher diagnostic accuracy for hilar biliary invasion of ampullary cancer than the combination of thickening and enhancement of the bile duct wall on CECT and biliary biopsy results (*P* value = 0.027, 0.017).

Adverse events

The adverse events are listed in Table 2. Postendoscopic ampullectomy bleeding occurred in two patients. Both patients improved with endoscopic hemostasis and transfusion. PEP occurred in three patients, all of whom improved with conservative treatment.

DISCUSSION

In this study, we investigated appropriate methods for diagnosing hilar biliary invasion of ampullary cancer. Hilar biliary invasion was not observed in all ampullary cancer patients. Although some false-positive results were obtained with each method, the diagnostic accuracy of the combination of partial

Table 2 Adverse events of treatment

Adverse event	*n*
Post-endoscopic ampullectomy bleeding	
Mild	0
Moderate	2
Severe	0
Post-ERC pancreatitis	
Mild	0
Moderate	3
Severe	0

ERC: Endoscopic retrograde cholangiography.

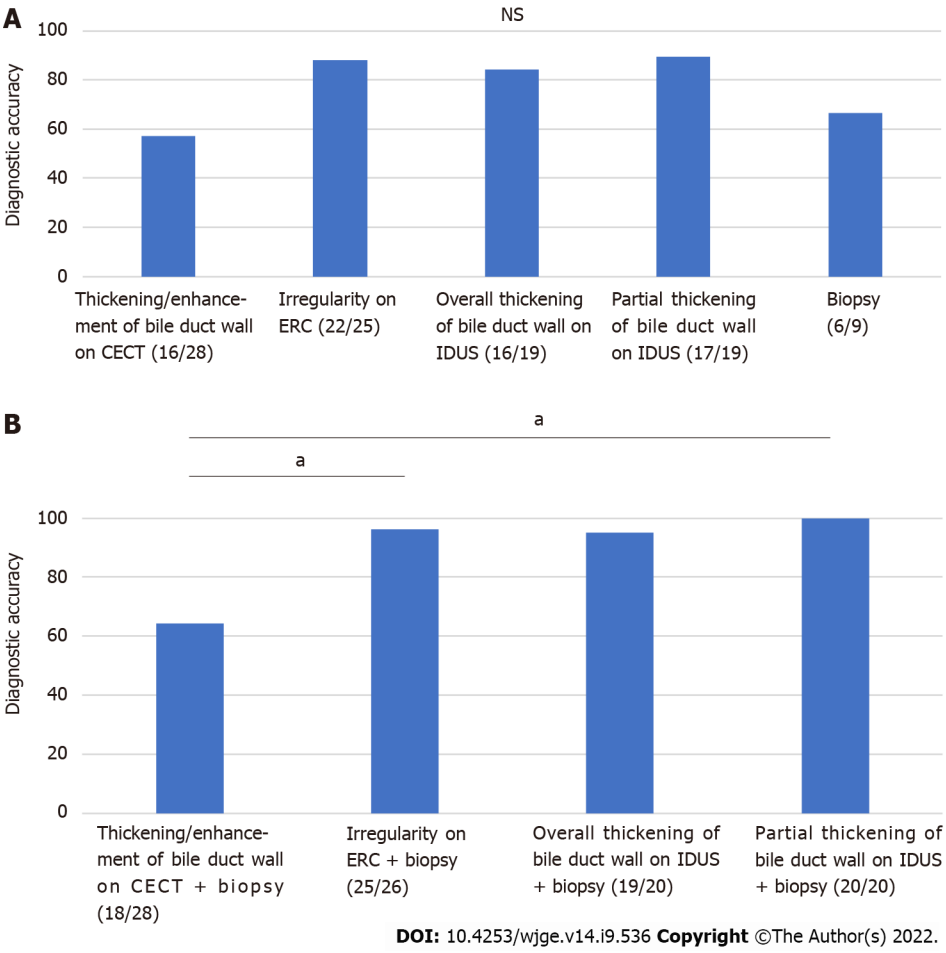


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Figure 3 Comparison of methods for diagnosing hilar biliary invasion of ampullary cancer in patients without biliary stents. A: Partial thickening of the bile duct wall on IDUS showed the highest diagnostic accuracy; B: Among the various combinations (imaging findings and biliary biopsy results) for diagnosing hilar biliary invasion, partial thickening of the bile duct wall on IDUS + biliary biopsy results showed the highest diagnostic accuracy. [a]*P* < 0.05. CECT: Contrast-enhanced computed tomography; ERC: Endoscopic retrograde cholangiography; IDUS: Intraductal ultrasonography; NS: Not significant.

thickening of the bile duct wall on IDUS and hilar biliary biopsy results for hilar biliary invasion was 100% for patients without biliary stents. On the other hand, thickening and enhancement of the hilar bile duct wall on CECT was not effective for diagnosing this condition.

Ampullary cancer occasionally develops concurrently with upstream biliary ductal cancer[34,35]. However, as described in the introduction, hilar biliary invasion of resectable ampullary cancer has rarely been reported. In fact, hilar invasion of ampullary cancer was not observed in this study. In past reports that have described the results of treatment or surgery for ampullary cancer, pancreaticobiliary

type, lymph node metastasis, advanced T stage, and large tumors were identified as risk factors for poor prognosis[36-41]. Hilar biliary invasion was not listed as a risk factor in these reports. Taking the risk of PEP into consideration, it is possible that investigation of hilar biliary invasion in ampullary cancer is not necessary.

Thickening of the bile duct wall on CECT has been reported in cholestasis caused by several diseases (for example, cholangitis, common bile duct stones, pancreatitis and malignant biliary stricture)[42]. In a past systematic review and meta-analysis, the diagnostic accuracy of computed tomography (CT) for assessing the extent of bile duct invasion was 64%-96%[13]. In this study, the diagnostic accuracy of CECT for assessing hilar biliary invasion of ampullary cancer was lower than that reported in a previous meta-analysis. Regarding the CECT findings of ampullary cancer, papillary bulging and organ invasion have been identified as predictive factors of tumor recurrence or poor survival[43]. However, hilar bile duct wall thickness was not mentioned in the associated study. Thickening and enhancement of the hilar bile duct wall on CECT was not useful. It is thought that ampullary cancer exists at the exit of the bile duct and that the tumors more often close the biliary duct than other biliary diseases. This closure leads to thickening of the hilar bile duct wall; however, in this study, ampullary cancer did not invade the hilar bile duct.

The diagnostic accuracy of IDUS was higher among those patients without biliary stents. Biliary drainage can cause thickening of the bile duct wall, and IDUS should be performed before biliary drainage. Thickening on the cancerous portion of the bile duct wall has been reported to be heterogeneous and partially protruded[24-27,44]. In this study, partial thickening of the bile duct wall on IDUS showed the best accuracy among the investigated methods for diagnosing hilar invasion of ampullary cancer in patients without a biliary stent. Naitoh *et al*[45] reported that bile duct wall thickening in the nonstricture region was unremarkable in bile duct cancer patients. However, false-positive cases (diameter of the hilar bile duct wall from 2-3.3 mm) were observed in this study. Therefore, the evaluation of the nonstricture portion on IDUS in patients with ampullary cancer is not believed to be equivalent to that in patients with common bile duct cancer. Therefore, the detection of partial thickening of the bile duct wall should be combined with other methods.

False-positive hilar biliary biopsy results were found in three cases. Although this number is low, such results might influence the operative method. Therefore, false positives in hilar biliary biopsy should be avoided. Regarding the reason for these false positives, it is highly likely that biopsy forceps contact the ampullary cancer. The efficacy of cholangioscopy in diagnosing biliary lesions has been reported[46-56]. However, passing the ampullary cancer is difficult with cholangioscopy. To avoid contact of the biopsy forceps with the tumor and to improve the diagnostic accuracy of hilar biliary biopsy for ampullary cancer patients, biliary biopsy with a catheter that introduces biopsy forceps could be useful[30,31]. When biliary biopsy with a catheter is unavailable, the combination of biliary biopsy and IDUS should be considered.

This study has some limitations. First, this was a retrospective study performed at a single institution. A multicenter prospective study is needed to verify the results of this study. Second, a few patients underwent all examinations (CECT, ERC, IDUS, and biliary biopsy). In future studies, a higher number of cases would be desirable. Third, as described above, ampullary cancer patients with hilar biliary invasion were not included in this study. To improve the false-negative rate, a study involving cases of hilar biliary invasion is needed.

CONCLUSION

Although false-positive results were obtained with each method, the combination of partial thickening of the bile duct on IDUS and biliary biopsy results was useful for diagnosing hilar biliary invasion of ampullary cancer. In addition, it is recommended that hilar biliary biopsy be performed through a catheter to avoid contamination from the cancer. However, hilar invasion of ampullary cancer is rare, and the risk of PEP from hilar investigation exists. Therefore, hilar investigation might be unnecessary for ampullary cancer patients.

ARTICLE HIGHLIGHTS

Research background

The standard treatment for ampullary cancer is pancreaticoduodenectomy or focal ampullectomy. Before resection, it is important to accurately diagnose the biliary invasion of ampullary cancer. However, the method that accurately evaluates hilar invasion of ampullary cancer is unknown.

Research motivation

Several methods [contrast-enhanced computed tomography (CECT), endoscopic retrograde cholangiography (ERC), intraductal ultrasonography (IDUS), biliary biopsy] can be used to diagnose the range

of ampullary cancer invasion. However, detailed data of these methods for diagnosing the biliary invasion range of ampullary cancer have not been previously reported. Therefore, presurgical examination is not established in ampullary cancer patients.

Research objectives

To reveal the necessity of hilar investigation in ampullary cancer and a useful method for diagnosing whether ampullary cancer invades the hilar biliary duct.

Research methods

Diagnosability was compared between CECT, ERC, IDUS, and biliary biopsy in ampullary cancer patients who underwent pancreaticoduodenectomy or focal ampullectomy.

Research results

The combination of biliary biopsy results and partial thickening of the bile duct wall on IDUS was efficient for diagnosing hilar invasion of ampullary cancer.

Research conclusions

Although false positives were observed for each method, hilar invasion was appropriately diagnosed based on the combination of biliary biopsy results and partial thickening of the bile duct wall on IDUS. However, hilar biliary invasion is rare in ampullary cancer. Therefore, hilar investigation might be unnecessary for ampullary cancer patients.

Research perspectives

The results of this study contribute to the establishment of a systematic method for diagnosing hilar invasion and selecting treatments for ampullary cancer patients.

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FOOTNOTES

Author contributions: Takagi T and Sugimoto M wrote the paper and designed and performed the study; Ohira H designed and oversaw the study; Suzuki R, Konno N, Asama H, Hikichi T, Nakamura J, Takasumi M, Sato Y, Irie H, Hashimoto M, Kato T, Kobashi R, and Yanagita T provided clinical advice; Hashimoto Y performed pathological diagnoses, and all authors read and approved the final version of the manuscript.

Institutional review board statement: This study was approved by the Institutional Review Board of Fukushima Medical University (approval number: 2453).

Informed consent statement: The patients were not required to give informed consent because this study "Screening for Hilar Biliary Invasion in Ampullary Cancer Patients" used anonymous clinical data obtained after each patient had agreed to medical activities by written consent. For full disclosure, the details of this study are published on the home page of Fukushima Medical University.

Conflict-of-interest statement: All authors declare that they have no competing interests.

Data sharing statement: The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic therapy using a self-expandable metallic stent with an anti-migration system for postorthotopic liver transplantation anastomotic biliary stricture

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Abstract

BACKGROUND

Endoscopic therapy using multiple plastic stents (MPSs) is the standard therapy for postorthotopic liver transplantation (p-OLT) anastomotic biliary stricture (ABS). However, this approach demands repeated procedures. Recent studies us-ing fully covered self-expandable metallic stents (FCSEMS) have shown en-couraging results, but migration occurs in 10% to 40% of cases. The objective of this retrospective study was to evaluate the efficacy of endoscopic treatment using FCSEMS with an anti-migration system (Am-FCSEMS) in patients with p-OLT ABS.

AIM

To evaluate the efficacy of endoscopic treatment using an Am-FCSEMS in patients with p-OLT ABS.

METHODS

This study was conducted in a private tertiary care centre in São Paulo, Brazil and was approved by our institution's Human Research Committee. From April 2018 to October 2020, regardless of previous endoscopic treatment (MPS or FCSEMS), 17 patients with p-OLT ABS and indications for endoscopic therapy were in-cluded in this study. The exclusion criteria were pregnancy, nonanastomotic

biliary or hilar stricture, hepatic artery stenosis/thrombosis, isolated biliary fistulae, a distance shorter than 2 cm from the stricture to the hepatic hilum, and patient refusal. The primary endpoint was the efficacy of p-OLT ABS endoscopic treatment using an Am-FCSEMS that re-mained in place for a 12-mo period. Biliary sphincterotomy was performed in patients with native papilla, and an Am-FCSEMS (10 mm in final diameter and 60 or 80 mm in length) was placed (Hanarostent™ MI Tech, Co). Balloon stricture dilation was performed only if necessary to introduce the stent.

RESULTS

Three patients were excluded due to loss to follow-up before stent removal. Among the 14 patients included and followed, 7 were women, and the average age was 56 years (range: 28-76). The average period of Am-FCSEMS placement was 362 ± 109 d. Technical success occurred in all 14 patients (100%). There were no cases of distal stent migration. Complete resolution of the stricture occurred in 13/14 patients (92.85%). Adverse events occurred in 3/14 patients (21.42%): 2 patients with mild acute pancreatitis (14.28%) and 1 patient (7.14%) with stent dysfunction (occlusion by biliary sludge and stones, which was treated endoscopically without the need for stent removal). No deaths occurred related to therapy. All stents were removed using foreign body forceps or snares without difficulty. After Am-FCSEMS removal, all 13 patients who had ABS resolution were followed-up for an average of 411 ± 172 d, and there was no stricture recurrence or need for further endoscopic therapy.

CONCLUSION

In this retrospective study, endoscopy therapy using an Am-FCSEMS for p-OLT ABS was safe and effective, with a high stricture re-solution rate that was probably due to the absence of stent migration.

Key Words: Liver transplantation; Endoscopy; Endoscopic retrograde cholangiopancreatography; Biliary strictures; Self-expandable metallic biliary stents

Core Tip: This retrospective study evaluated the efficacy of endoscopic treatment using an anti-migration fully covered self-expandable metallic stents (Am-FCSEMS) in patients with postorthotopic liver transplantation (p-OLT) anastomotic biliary stricture (ABS). Technical success occurred in all patients (100%). Stricture resolution occurred in 13/14 patients (92.85%). Adverse events occurred in 3/14 patients (21.42%). There were no cases of distal stent migration. After Am-FCSEMS removal, all 13 patients who had ABS resolution were followed-up for an average of 411 d, and there was no stricture recurrence or need for further endoscopic therapy. Endoscopic therapy using an Am-FCSEMS for p-OLT ABS is safe and effective, with a high stricture resolution rate, probably due to the absence of stent migration.

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INTRODUCTION

Biliary tract lesions are common postoperative adverse events (AEs) after orthotopic liver transplantation (OLT). Anastomotic biliary strictures (ABSs) occur most frequently and are responsible for approximately 40% of all complications after OLT[1-4].

Endoscopic balloon dilation followed by placement of side-by-side multiple plastic stents (MPSs) in repeated procedures every 3-4 mo, up to 12 mo, is the standard treatment for ABS. This treatment strategy has a high success rate, ranging from 70% to 100%[1,5].

Despite such a high success rate, this strategy demands repeated procedures[1,6-9]. Recent studies using fully covered self-expandable metallic stents (FCSEMS) have shown encouraging results, with resolution rates similar to those observed with the MPS strategy[5,7,10]. However, a high FCSEMS migration rate of between 10% and 40% has been reported, which is a possible limitation for its use[5-7, 10].

We hypothesized that a FCSEMS with an anti-migration system (Am-FCSEMS) could be an alternative for postorthotopic-OLT (p-OLT) ABS treatment. Recently, a study with promising results compared the use of an Am-FCSEMS with other types of conventional metallic stents in regards to the p-OLT ABS resolution rate and their respective migration rates[11].

The objective of this study was to evaluate the efficacy of endoscopic treatment using an Am-FCSEMS in patients with p-OLT ABS.

MATERIALS AND METHODS

This study was conducted at Hospital Israelita Albert Einstein (HIAE), São Paulo, Brazil. HIAE is a private tertiary care referral centre where approximately 150 OLTs are performed yearly.

Patients

From April 2018 to October 2020, 17 patients between 18 and 76 years of age diagnosed with p-OLT ABS who were referred to the endoscopy unit were considered for inclusion in this retrospective study, regardless of previous endoscopic treatment (MPS or FCSEMS). The exclusion criteria were pregnancy, nonanastomotic biliary or hilar stricture, hepatic artery stenosis/thrombosis, isolated biliary fistulae, and patient refusal. To avoid the risk of biliary intrahepatic duct occlusion secondary to stent placement, a distance shorter than 2 cm from the stricture to the hepatic hilum was also considered an exclusion criterion.

This study was conducted in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and was approved by our institution's Human Research Committee. The patients provided written informed consent prior to inclusion in the study.

Procedures

Endoscopic retrograde cholangiopancreatography (ERCP) was performed using a therapeutic video duodenoscope (TJF-180 Olympus Optical Co., Ltd., Tokyo, Japan) with patients under monitored anaesthesia. After selective biliary cannulation, cholangiography was performed for the evaluation and characterization of biliary stricture, followed by the passage of a guidewire. After positioning the guidewire, biliary sphincterotomy was performed in patients with native papilla, and an Am-FCSEMS (10 mm in final diameter and 60 or 80 mm in length, BCT Hanarostent™ M.I. Tech, Co.) was placed (Figure 1A and B). Balloon dilation of the stricture was performed only if necessary to introduce the stent. According to the physician's choice, the length of the stent was determined during cholangiography to place the proximal end between the stricture and the hepatic hilum and the distal end in the duodenum. Patients were followed up for clinical signs of biliary obstruction and scheduled to have the stent removed after 12 mo if no complications occurred.

Endpoints

The primary study endpoint was the efficacy of the endoscopic treatment of p-OLT ABS using an Am-FCSEMS for a 12-mo period. Efficacy was evaluated based on ABS resolution. After stent removal, the biliary stricture was considered resolved if there was no stricture observed on cholangiography or a minimum stricture that allowed the passage of a 12-mm inflated extractor balloon without difficulty. Secondary endpoints were technical success (defined as stent placement), adverse effects related to ERCP (bleeding or pancreatitis), and stent dysfunction (migration or obstruction).

RESULTS

A total of 17 patients were included. Three patients were excluded due to loss to follow-up before stent removal (12 mo) (Figure 2). The average age of the 14 patients included and followed was 56 years (range: 28-76); 7 women had an average age of 42 ± 11.2 years, and 7 men had an average age of 69 ± 5.8 years. Patient characteristics are shown in Table 1. Among the 14 patients, 8 (57.14%) had already undergone treatment with FCSEMS and/or MPSs, but endoscopic management was considered unsuccessful, with an average number of procedures before inclusion in this study of 2.25 ± 1.04 (range: 1-4). The other 6 patients (42.85%) received an Am-FCSEMS as the first treatment. Regardless of previous treatment, the average interval from p-OLT to the first ERCP was 116 wk (range: 4-570). The average duration of placement of an Am-FCSEMS in this study was 362 ± 109 d (range: 226-609). The length of stent placement was 6 cm in 8 patients and 8 cm in 6 patients. Technical success (stent placement) occurred in all 14 patients (100%). The clinical follow-up after stent removal was 411 ± 172 d (range: 55-692). All stents were removed using foreign body forceps or snares without any technical difficulty (Figure 1C).

Table 1 Demographics of patients and baseline characteristics

Overall patient characteristics	Results
No. of patients, *n*	14
Gender, female sex, *n* (%)	7 (50)
Age (yr), mean (range)	56 (28-76)
Cause of liver transplant: *n*	
HBV	2
HBV + HCV	1
Alcohol	3
Cryptogenic	2
NASH	1
Autoimmune hepatitis	2
Primary biliary cirrhosis	1
Familial amyloidosis	1
Primary hyperoxaluria	1
Presence of HCC: *n*	4
Time from OLT to ERCP (wk)	
mean ± SD	116 ± 156
Median	45
Range	4-570
Patients with previous endoscopic treatment before Am-FCSEMS, *n* (%)	8 (57.14)
Procedures before Am-FCSEMS (mean)	2.25
Patients with no previous endoscopic treatment, *n* (%)	6 (42.86)

HBV: Hepatitis B virus; HCV: Hepatitis C virus; NASH: Nonalcoholic steatohepatitis; HCC: Hepatocellular carcinoma; ERCP: Endoscopic retrograde cholangiopancreatography; Am-FCSEMS: Fully covered self-expandable metal stents with anti-migration flaps.

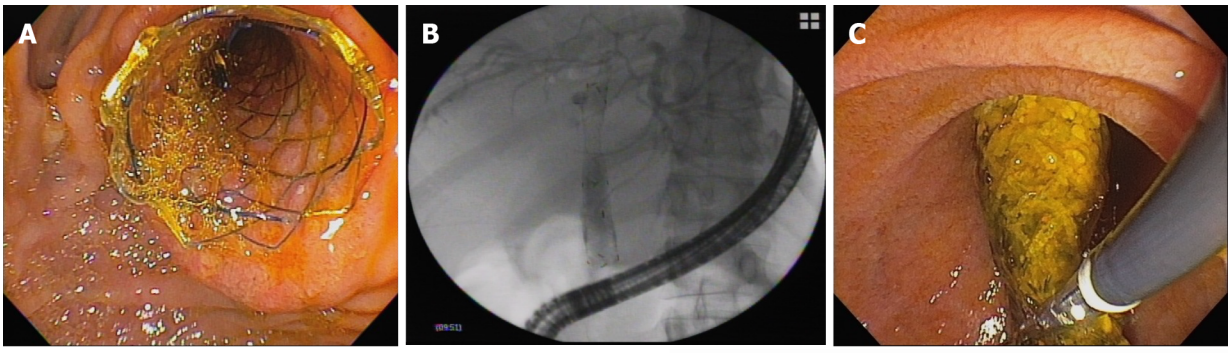

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Figure 1 Images of the fully covered self-expandable metallic stent with an anti-migration system or flaps. A: Endoscopic view of the stent; B: Radiographic view of the stent in the biliary tract; C: Removal of the stent.

Complete resolution of the stricture occurred in 13/14 patients (92.85%). Only 1 patient (7.14%) experienced endoscopic treatment failure after 338 d with the stent in place, which was determined by cholangiography as persistence of stricture. This patient was referred for endoscopic treatment using MPSs for a longer period. AEs occurred in 3 out of 14 patients (21.42%). There were 2 patients (14.28%) with mild acute pancreatitis and 1 patient (7.14%) with stent dysfunction (occlusion by biliary sludge and stones with cholangitis), which was treated endoscopically without the need for stent removal. There was no distal migration of the stent in any patient (Table 2). There was no mortality related to ERCP and/or endoscopic therapy with the stent. After removal of the Am-FCSEMS, all 13 patients who

Table 2 Overall results

Overall results	
No. of patients, *n*	14
Technical success, *n* (%)	14 (100)
Stricture resolution, *n* (%)	13 (92.85)
Treatment failure, *n* (%)	1 (7.14)
Mean ALT before stent (U/L)	144
Mean ALT at the end of follow-up (U/L)	16
Mean total bilirubin before stent (mg/dL)	1. 88
Mean total bilirubin at the end of follow-up (mg/dL)	0. 49
Stricture recurrence, *n*	0
Stent migration	0
Other complications, *n* (%)	3 (21.42)
Acute pancreatitis	2 (14.28)
Stent occlusion	1 (7.14)
Mean follow-up after stent removal (d)	411 ± 172

ALT: Alanine aminotransferase.

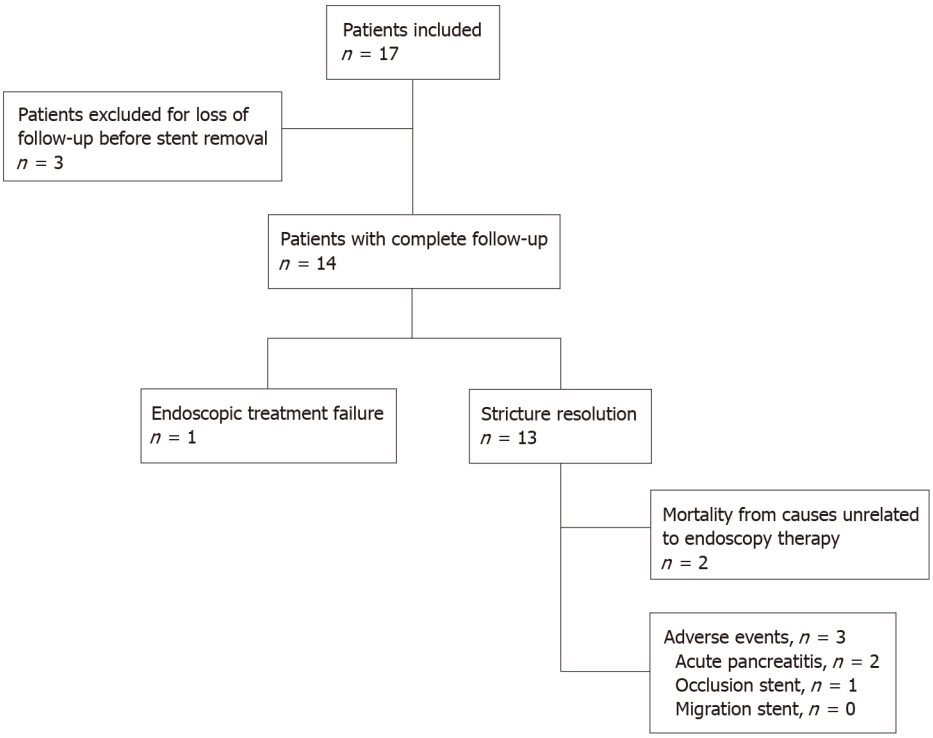

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Figure 2 Flowchart of the selection of patients in the study.

had ABS resolution were followed-up (411 ± 172 d), and there was no need for further endoscopic therapy or stricture recurrence. Two patients died from causes unrelated to endoscopy therapy.

DISCUSSION

Our present study shows that p-OLT ABS treatment with an Am-FCSEMS is effective and safe, with a stricture resolution rate of 92.85%, which is comparable to the results of other studies involving MPSs[5,9,12] and FCSEMSs[5,7,13]. In our study, the average time between liver transplantation and endoscopy therapy for ABS was lengthy (116 wk), which may have impacted the results and thus, is a possible limitation of this study[3,6,8]. Nevertheless, our results were comparable with those of other studies that used this anti-migration stent model[11].

The longer stent maintenance period (12 mo) in our study in relation to other studies with metallic stents[2,7] and the absence of migration possibly related to the antimigration mechanism may have contributed to the favourable result observed in our patients.

The technical success rate of 100% in this series, which is comparable to that in other studies[6,12,14], demonstrates the applicability of this technique. No patients experienced distal migration of the stent. As described in previous studies, the main disadvantage of using FCSEMS is the high migration rate of up to 37.5%[10,12,14,15]. It is possible that treatment with an Am-FCSEMS may present better results due to the lower risk of migration and longer stent patency. Although in our study assessment of costs was not an included objective, it is possible that since this stent has a lower migration rate its use could result in a lower number of procedures and thus lower costs, but this hypothesis should be verified in future controlled studies.

The AEs observed with ERCP-related therapy and/or stenting were mild pancreatitis and delayed stent obstruction. All patients in whom the stent was placed underwent biliary sphincterotomy, and mild acute pancreatitis was related to the ERCP procedure in 2 out of the 14 patients (14.2%). Despite this higher rate of complications compared to that in the literature[5-7,13], these patients underwent successful clinical treatment. Stent dysfunction (obstruction) occurred late and was caused by biliary sludge or stones, with jaundice and cholangitis occurring in only one patient (7.1%). This complication and its endoscopic treatment with or without stent replacement is described in the literature[5,6]. This patient was treated with antibiotics and endoscopy without the need for stent replacement.

No complications occurred during stent removal. In this study, no serious complications or deaths related to endoscopic treatment were reported. The average follow-up of patients who had stricture resolution after removal of the metallic stent was 411 d. There was no ABS recurrence during follow-up. This positive result may be related to the prolonged maintenance of the metallic stent, which was longer than 6 mo[2,5].

Considering the treatment of patients with p-OLT ABS, the use of FCSEMSs may be an interesting alternative in relation to MPS therapy, considering FCSEMS placement presents comparable results with fewer ERCP procedures[4,5,7,10]. However, spontaneous stent migration may be a limitation of FCSEMS placement[10,12,14].

This retrospective study has some limitations, such as a small sample size from a single centre. Another limiting point for this study is the lack of a control group. However, our results showed that treatment with Am-FCSEMS can be an alternative for patients with p-OLT ABS. Therefore, prospective and comparative studies should be encouraged to evaluate the efficacy of endoscopic treatment using Am-FCSEMS versus MPSs. Nevertheless, we present similar results for the resolution of ABS compared to those in other studies using MPSs and FCSEMSs as well as a recent study using an Am-FCSEMS. In this series, the advantage of treatment using an Am-FCSEMS in relation to treatment with MPSs was the need for only two ERCP procedures over 12 mo, while the advantage in relation to FCSEMS therapy was the absence of migration.

CONCLUSION

In conclusion, in this retrospective study, endoscopy therapy using an Am-FCSEMS or flaps for p-OLT ABS is safe and effective, with the stricture´s high-resolution rate probably being due to the absence of stent migration.

ARTICLE HIGHLIGHTS

Research background

Endoscopic therapy using multiple plastic stents is the standard therapy for postorthotopic liver transplantation (p-OLT) anastomotic biliary stricture (ABS). However, this approach demands repeated procedures. Recent studies using fully covered self-expandable metallic stents (FCSEMS) have shown encouraging results, but migration occurs in 10% to 40% of cases. We hypothesized that a FCSEMS with an anti-migration system (Am-FCSEMS) could be an alternative for treatment in patients with p-OLT ABS.

Research motivation
The efficacy of treatment using an Am-FCSEMS for p-OLT ABS is not yet well established. The outcomes of endoscopic treatment using this type of stent have become clinically relevant.

Research objectives
This study aimed to evaluate the efficacy of endoscopic treatment using an Am-FCSEMS in patients with p-OLT ABS.

Research methods
This study was conducted in a private tertiary care centre in São Paulo, Brazil. From April 2018 to October 2020, patients with p-OLT ABS and indications for endoscopic therapy were included in this study, and an Am-FCSEMS (10 mm in final diameter and 60 or 80 mm in length) was placed (Hanarostent MI Tech, Co).

Research results
Technical success occurred in all 14 patients (100%). There were no cases of distal stent migration. Complete resolution of the stricture occurred in 13/14 patients (92.85%). Adverse events occurred in 3/14 patients (21.42%): 2 patients with mild acute pancreatitis and 1 patient with stent dysfunction (occlusion). No deaths occurred related to therapy. After Am-FCSEMS removal, all 13 patients who had ABS resolution were followed-up for an average of 411 ± 172 d, and there was no stricture recurrence or need for further endoscopic therapy.

Research conclusions
Endoscopy therapy using an Am-FCSEMS for p-OLT ABS is safe and effective, with the stricture´s high-resolution rate probably being due to the absence of stent migration.

Research perspectives
This study shows that treatment using Am-FCSEMS has a high rate of stenosis resolution, probably due to the absence of stent migration, and may result in a lower number of procedures.

FOOTNOTES

Author contributions: Pinheiro LW, Martins FP, Contini MLC, and De Paulo GA contributed to the data acquisition; Pinheiro LW, De Paulo GA, Ferrari AP, and Della Libera E contributed to the data analysis and interpretation; Pinheiro LW contributed to the elaboration of article draft; Martins FP and Contini MLC contributed to the elaboration and review of article draft, critical review for important intellectual content; De Paulo GA contributed to the critical review of final paper for important intellectual content; Ferrari AP and Della Libera E contributed to the critical review and approval of the final submitted version.

Institutional review board statement: This retrospective study was approved by the Institution's Human Research Committee of Hospital Israelita Albert Einstein (No. 37755020.3.0000.0071).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Observational Study

Clinical profile, diagnostic yield, and procedural outcomes of single balloon enteroscopy: A tertiary care hospital experience

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Abstract

BACKGROUND

Single balloon enteroscopy (SBE) allows ease of access for small bowel visualization and has multiple diagnostic and therapeutic indications. It provides the advantage of performing various therapeutic interventions alongside the diagnostic procedure. SBE has also been considered a relatively safe procedure with no major complications.

AIM

To investigate the indications, safety, and clinical yield of SBE, and determine its effect on disease outcome.

METHODS

A retrospective, descriptive study was conducted at a tertiary care hospital in Karachi, Pakistan. Medical records of 56 adult patients (≥ 18 years) who underwent SBE between July 2013 and December 2021 were reviewed and data were collected using a structured proforma. A descriptive analysis of the variables was performed using Statistical Package of Social Sciences Version 19. Results are reported as the mean ± SD for quantitative variables and numbers and percentages for qualitative variables. Missing data are reported as unknown.

RESULTS

A total of 56 patients who underwent 61 SBE procedures were included. The mean age was 50.93 ± 16.16 years, with 53.6% of them being males. Hypertension (39.3%) and diabetes mellitus (25.0%) were the most common pre-existing comorbidities. Obscure gastrointestinal bleed (39.3%) was the most common indication for enteroscopy, followed by chronic diarrhea (19.7%) and unexplained anemia (16.4%). The majority of procedures were performed in the endoscopy

suite (90.2%) under monitored anaesthesia care (93.4%). Most procedures were diagnostic (91.8%) and completed without complications (95.1%). The depth of examination ranged from 95 cm to 500 cm with a mean of 282.05 ± 90.04 cm. The most common findings were inflammation and ulcerations (29.5%), followed by masses (19.7%) and vascular malformations (14.8%). As a result of the findings, a new diagnosis was made in 47.5% of the cases and a previous one was ruled out in 24.6% of them; 65.6% of the cases had a change in management.

CONCLUSION

SBE is a suitable modality for investigating diseases in the small bowel. It is shown to be technically efficient and reasonably safe and is associated with high diagnostic and therapeutic yield.

Key Words: Single balloon enteroscopy; Small bowel diseases; Gastrointestinal bleed; Small bowel endoscopy; Small bowel; Balloon-assisted enteroscopy

Core Tip: Single balloon enteroscopy (SBE) is a safe and effective modality which allows ease of access for small bowel visualization. The procedure has multiple diagnostic and therapeutic indications. However, there is insufficient data published reporting its efficacy and impact. In this study, we analysed our single centre data of adults who underwent SBE between 2013 and 2021. We report patient demographics, procedure indications, and procedure findings. Based on our results, we can assess the indications, safety, and clinical yield of SBE, and determine its effect on disease outcome.

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INTRODUCTION

For decades, gastroenterologists have been challenged by the lack of proper visualization provided by standard endoscopies to the small intestine, with many of its areas being difficult to access without an intra-operative endoscopy procedure[1]. Enteroscopy has been a significant breakthrough in this field, allowing access to most of the small bowel using endoscopic techniques without the need for surgery [2]. Initially, Push enteroscopy was established in the 1980s. However, it was associated with a limited depth of penetration into the small bowel, up till the level of the proximal jejunum, due to difficulty in manoeuvring it further. This was followed by the advent of the push-and-pull enteroscopy in 2001, also known as double balloon enteroscopy (DBE). DBE, as its name suggests, consists of two balloons: One on the tip of the enteroscope and the other on an overtube at the scope's distal end. The controlled inflation and deflation of the balloons allow the enteroscope to properly proceed without causing over-looping of the intestine. The volumes and pressures in the balloons are also measurable and are monitored throughout the procedure. As a result, DBE furthered the reach of the enteroscope and was seen to improve diagnostic yield, thereby overcoming the limitations of its preceding modality[1-4].

The single balloon enteroscopy (SBE) system was launched in 2007 as an alternative to DBE. SBE consists of only one balloon attached to the overtube at the scope's distal end and is relatively easier to use. The tip of the enteroscope is angled during withdrawal of the scope in the small bowel to achieve stable positioning and insufflation of the overtube is performed using a pressure-controlled pump[5]. Both methods have been shown to yield significant and similar therapeutic and diagnostic yield[6-9].

Small bowel capsule endoscopy is currently the first-line recommended technique for investigation of the small bowel in patients with obscure gastrointestinal bleed. This is often used as a preliminary examination prior to device assisted enteroscopy (DAE) if further investigation is clinically indicated[10, 11]. According to the most recent European Society of Gastrointestinal Endoscopy guidelines, DAE is also particularly recommended in patients with co-morbidities and/or those undergoing a therapeutic procedure since all endoscopic therapeutic procedures can be undertaken at the time of DAE[12].

The most common indication for small bowel enteroscopy is obscure gastrointestinal bleeding, defined as bleeding from the gastrointestinal (GI) tract that persists or recurs without an obvious cause after esophagogastroduodenoscopy, colonoscopy, and radiographic evaluation of the small bowel[13]. Other indications include chronic diarrhea, Crohn's disease, refractory celiac disease, small bowel malignancies, suspected nonsteroidal anti-inflammatory drug-induced small bowel injury, suspicion of

small bowel obstruction, and detection of polyps in patients with polyposis syndromes[7]. Enteroscopy can also be performed in patients presenting with several different symptoms, with no specific diagnostic results yielding from regular endoscopy. The advantage of SBE compared to other techniques for visualizing the small bowel, such as capsule endoscopy and radiologic methods, is in the ability to perform a wide variety of therapeutic interventions alongside the diagnostic procedure[14]. SBE has also been considered a relatively safe procedure with no major complications. The safety profile has been shown to match that of DBE overall, and the only major complications seen have been those that have resulted due to perforations[15].

While the existing literature has highlighted great diagnostic and therapeutic benefits of SBE, the data regarding its outcomes are scarce and not widely generalizable. The equipment costs and specialized training requirements could be reasons as to why SBE is not a commonly practiced procedure.

There is currently limited published data from developing countries detailing enteroscopy utility and outcomes. We aimed to explore the role of small bowel push enteroscopy in our population and study its indications, safety, findings, complications, diagnostic yield, and effect on disease outcome, in order to increase the body of knowledge regarding this procedure.

MATERIALS AND METHODS

This was a retrospective observational study conducted in a tertiary care referral centre in Karachi, the largest and most populated metropolitan city of Pakistan. Ethical approval and exemption were granted by the Ethical Review Committee of the institution on December 31, 2020 (2020-5760-15324).

Medical records of all adult patients above the age of 18 years who underwent a SBE procedure at the Aga Khan University Hospital from July 3, 2013 to December 31, 2021 were identified by random sampling, using the hospital's information medical record system. A chart review was conducted for all eligible patients. For each medical record, a proforma was completed regarding patient demographics, comorbidities, clinical presentation, medication history, procedure details, and enteroscopy and biopsy findings. In order to determine the procedure yield, a through chart review of the in- and out-patient hospital course was conducted (see Appendix: Enteroscopy questionnaire).

Our inclusion criteria were all adult patients over the age of 18 years who underwent a SBE procedure at the hospital within our study period. There were no exclusion criteria. All patients signed an informed consent form prior to the procedure (see Appendix: Consent form). Patient outcomes were defined as a change or otherwise in the patient's diagnosis and management as a result of the findings of the procedure.

A descriptive analysis was performed for patient demographics, clinical characteristics, and enteroscopy details. Data were analysed descriptively. Results are reported as the mean ± SD for quantitative variables and numbers and percentages for qualitative variables. Missing data are reported as unknown. Data were analysed using Statistical Package of Social Sciences (SPSS) Version 19. The statistical methods of this study were reviewed by Safia Awan of the Aga Khan University Hospital.

RESULTS

Our final study population comprised of a total of 56 patients (Table 1) who underwent a total of 61 procedures. The mean age of our sample was 50.93 ± 16.16 years, with the majority being males (53.6%, n = 30). Hypertension (39.3%, n = 22) and diabetes mellitus (25.0%, n = 14) were the most common pre-existing comorbidities. Prior medication use included antiplatelet (5.4%, n = 3) and non-steroidal anti-inflammatory drug (3.6%, n = 2) therapy, which is known to be associated with GI injury such as obscure bleeding and inflammation[13-14]. No patient in our study sample was on anticoagulation medications.

The clinical findings and outcomes of the 61 enteroscopy procedures are outlined in Table 2. Obscure gastrointestinal bleed was the most common enteroscopy indication (39.3%, n = 24), followed by chronic diarrhea (19.7%, n = 12). Other indications included unexplained anemia (16.4%, n = 10), enteric thickening and inflammatory changes on imaging (11.5%, n = 7), small intestinal space occupying lesion (11.5%, n = 7), persistent vomiting (9.8%, n = 6), weight loss (6.6%, n = 4), and malabsorption syndrome (6.6%, n = 4). Most of the procedures were performed in the endoscopy suite (90.2%, n = 55) under monitored anaesthesia care (93.4%, n = 57). However, 9.8% (n = 6) of cases were done in the main operating room, with 8.2% (n = 5) due to patient comorbidities and 1.6% (n = 1) in conjunction with an additional surgical procedure.

The majority of the enteroscopy procedures were diagnostic (91.8%, n = 56). Interventions were carried out following 27.8% of the cases. Out of these, 13.1% (n = 8) were enteroscopic interventions like polypectomy, argon plasma coagulation, adrenaline sclerotherapy, hemoclip attachment and stent removal, 9.8% (n = 6) were surgical interventions, and 4.9% (n = 3) were radiological interventions like angioembolization, which followed post procedure.

Table 1 Patient characteristics (*n* = 56)

	mean ± SD	Median	Range
Age	50.93 ± 16.16	47	26-87
		n	%
Gender	Male	30	53.6
	Female	26	46.4
Comorbidities	Hypertension	22	39.3
	Diabetes mellitus	14	25
	Chronic kidney disease	6	10.7
	Chronic liver disease	4	7.1
	Ischemic heart disease	3	5.4
	Inflammatory bowel disease	3	5.4
	Cerebrovascular accident	2	3.6
	Asthma	2	3.6
	Rheumatoid arthritis	1	1.8
Prior medications	Antiplatelets	3	5.4
	Non-steroidal anti-inflammatory drugs	2	3.6
	Anticoagulation	0	0

The depth of the enteroscopy examination ranged from 95 cm to 500 cm with a mean of 282.05 ± 90.04 cm. Enteroscopy examination was normal in 44.3% (*n* = 27) of the cases, while inflammation and ulcerations were seen in 29.5% (*n* = 18), space occupying lesions and masses in 19.7% (*n* = 12), vascular malformations in 14.8% (*n* = 9), and active bleeding in 8.2% (*n* = 5). A biopsy was obtained in 33 (54.1%) cases and the results included non-specific inflammation (63.6%, *n* = 21), malignancies or dysplasia (27.2% *n* = 9), villous atrophy (3.0% *n* = 1), and presence of Giardia (3.0%, *n* = 1). Out of the malignancies/dysplasia, 15.2% (*n* = 5) of the cases were adenocarcinoma, and there was one case each of adenomatous polyp (3.0%), inflammatory polyp (3.0%), hamartomous polyp (3.0%), and lymphoma (3.0%).

There was no mortality recorded in our study. Most procedures were successfully completed without any complications, while complications were seen in three (4.9%) procedures. All complications were either conservatively managed or resolved spontaneously following the procedure.

One patient had premature ventricular contractions during the procedure which were conservatively managed and resolved while another developed hemodynamic instability which resolved spontaneously post procedure. The third patient developed aspiration pneumonia post procedure which resolved with antibiotics.

The clinical yield of the SBE procedures in our study was determined by quantifying the change in diagnosis and management. A classification of a change in diagnosis was made when a diagnosis which was made prior to the enteroscopy procedure was either modified or disproven following the procedure findings. There was a change in diagnosis in 72.1% (*n* = 44) of the cases. Out of these, a new diagnosis was made in 47.5% (*n* = 29) of the cases (termed as positive changes) while a previous diagnosis was disproven in 24.6% (*n* = 15) (termed as negative changes). A classification of a change in management was made when a management plan which was made prior to the enteroscopy procedure was either modified or disproven following the procedure findings. There was a change in management in 65.6% (*n* = 40) of the cases.

DISCUSSION

Our study adds to the limited published literature regarding SBE experience from a tertiary care hospital in a developing country. A few studies analysing the indications, efficacy, outcomes, and safety of enteroscopy procedures have been carried out in various countries. The efficacy of SBE was also compared with that of double balloon enteroscopy in several retrospective studies and meta-analyses [16-20]. Moreels *et al*[21] conducted a case series in 2016 evaluating the therapeutic actions of SBE using a new prototype and highlighting its benefits. Studies have also been carried out to evaluate the efficacy of SBE in non-invasive evaluation of obscure gastrointestinal bleeding and Crohn's disease, but there

Table 2 Clinical variables of single balloon enteroscopy (*n* = 61)

		n	%
Enteroscopy indication	Obscure gastrointestinal bleeding	24	39.3
	Chronic diarrhea	12	19.7
	Unexplained anemia	10	16.4
	Enteric thickening/inflammatory changes on imaging	7	11.5
	Small intestinal space occupying lesion	7	11.5
	Persistent vomiting	6	9.8
	Weight loss	4	6.6
	Malabsorption syndrome	4	6.6
Procedure location	Endoscopy suite	55	90.2
	Operating room	6	9.8
Sedation	Monitored anaesthesia care	57	93.4
	General anaesthesia	4	6.6
Procedure	Diagnostic	56	91.8
	Therapeutic	5	8.2
	mean ± SD	Median	Range
Depth of procedure (cm)	282.05 ± 90.04	300	95-500
Enteroscopy findings	Normal	27	44.3
	Inflammation and ulcerations	18	29.5
	Space occupying lesions and masses	12	19.7
	Vascular malformations	9	14.8
	Bleeding	5	8.2
	Ascaris worm	1	1.6
Biopsy findings (*n* = 33)	Non-specific inflammation	21	63.6
	Malignancy/dysplasia		
	Adenocarcinoma	5	15.2
	Adenomatous polyp	1	3
	Inflammatory polyp	1	3
	Hamartomous polyp	1	3
	Lymphoma	1	3
	Villous atrophy	1	3
	Presence of Giardia	1	3
	Normal	1	3
Complications	Yes	3	4.9
	No	58	95.1
Change in diagnosis	Yes		
	Positive change	29	47.5
	Negative change	15	24.6
	No	17	27.9
Change in management	Yes	40	65.6
	No	21	34.4
Interventions	Enteroscopic		

Angioembolization	4	6.6
Argon plasma coagulation	3	4.9
Polypectomy	3	4.9
Adrenaline sclerotherapy	3	4.9
Red blood cell scintography	1	1.6
Surgical	6	9.8
Radiological	3	4.9

was a dearth of data describing experiences over many years for all cause indications, which additionally limits data providing information regarding the safety and efficacy of the procedure[22-24].

The demographics of our patient population are comparable to those of other studies from Korea and India, which reported a mean age of 50-55 years and the majority of males (52.9%-69.1%). However, a study conducted in the United States had a higher mean age at 62 ± 17 years[25]. In agreement with our results, published studies report obscure GI bleeding as the most common indication, ranging from 48% to 97%, in patients undergoing SBE. Other common indications included anemia, chronic diarrhea, lesions, polyposis, and Crohn's disease, amongst others, in various proportions[18,22,25].

Ulcers (19.6%), tumors (16.7%), and vascular malformations (14.7%) were the most common findings in a single-centre retrospective study conducted in China to test the diagnostic yield and safety of SBE [23]. Overall, the findings reported in the literature are similar and proportional to those seen in our study population.

We determined a high safety profile of SBE in our patients, with non-severe complications arising in only three (4.9%) of the cases, which were subsequently conservatively managed. There were no cases of severe complications reported in our patients. This is in accordance with the previous literature which shows a very low incidence of any adverse effects following SBE. A meta-analysis including four studies showed no evidence of any severe adverse effects such as bowel perforation, bleeding, or pancreatitis [26]. It has also been previously reported that the adverse effects seen in SBE procedures were comparable to those seen in DBE procedures, with both being marked as safe according to a single-centre retrospective analysis. However, the study accounted for a performance bias as all the procedures were carried out by a single endoscopist, who was trained in the procedure[20]. One study on the usage of emergency SBE concluded that the incidence of adverse effects was lower when general anaesthesia was used as compared to when it was performed under conscious sedation[23]. Our SBE procedures were always performed by the same team of endoscopists with significant expertise as well, resulting in no major adverse effects.

A similar study reported a mean depth as 23 ± 87 cm beyond the ligament of Treitz with a range of 20-400 cm, in accordance with our findings[22]. In a randomized controlled trial, the mean depth of insertion of anterograde SBE procedures was found to be 203.8 cm[24]. A previous study has also been shown to explain a method used by endoscopists to assess the depth of insertion which is based on advancement with each push-and-pull manoeuvre in cases of DBE[25].

In our study, 65.6% (n = 40) of the procedures resulted in a change in management and 72.1% (n = 44) had a change in diagnosis following enteroscopy findings. The literature reports diagnostic yields of SBE ranging from 47% to 65%, and therapeutic yields from 25% to 42%[18,20,22,25].

A single centre retrospective study published in 2020 studied the safety and diagnostic yield of capsule endoscopy in the investigation of obscure gastrointestinal bleeds[10]. The study population included 58.6% of males with a mean age of 67.7 ± 14.4 years. The results showed a diagnostic yield of 73.8%, revealing clinically significant bleeds which were missed at gastroscopy or colonoscopy in 30.3% of patients.

The limitations of our study include a retrospective, single-centre analysis. While our sample size is relatively small compared to that of other similar studies, it included all patients who underwent a SBE procedure at our institution over an 8-year period. However, our study findings are solely representative of a South Asian population in a low-middle income country (LMIC). Our study also notes a lack of a standardized reporting template for SBE depth of examination that may be used internationally.

Our observed findings can be used to guide further research, as the current literature on the clinical indications, safety profile, diagnostic yield, and patient outcomes of enteroscopy is not sufficient to provide the basis for the development of guidelines, especially in LMICs. Additional prospective studies with larger sample sizes are recommended to grasp a thorough understanding of the indications and efficacy of SBE. Long-term follow-up studies will also be beneficial in demonstrating the clinical impact of SBE.

CONCLUSION

Our study reports an encouraging single centre tertiary care experience of SBE over an 8-year period. We conclude that SBE is a safe and effective method with a high clinical impact on precise diagnosis and management of small bowel diseases.

ARTICLE HIGHLIGHTS

Research background

Single balloon enteroscopy (SBE) is a procedure that has greatly improved the access to small bowel visualization, particularly of the mid and distal parts of the small bowel. In addition to being used as a diagnostic tool, SBE can also be used to perform a number of therapeutic interventions. SBE is a relatively safe procedure with a low incidence of complications and a good diagnostic and therapeutic yield. One of the most common indications generally seen is intestinal bleeding.

Research motivation

Since SBE is a relatively new procedure, there is still an absence of viable literature about it from the developing world countries like Pakistan. Due to the good yields from this procedure, proper adaptation of this technique in these places can greatly be used to improve healthcare outcomes particularly pertaining to small bowel problems by improving timely diagnosis and management.

Research objectives

To investigate the indications, procedures, findings, and safety of SBE procedures and to correlate their effects on the disease outcomes.

Research methods

We performed a retrospective descriptive study at a tertiary care hospital in Pakistan and investigated all the SBE procedures carried out between July 2013 and December 2021. A total of 56 patients underwent 61 SBE procedures during this time period. We collected data using patient files and electronic health records using a structured proforma. It was interpreted and then categorized and analyzed using the SPSS software.

Research results

Our study population consisted of 56 patients who underwent 61 SBE procedures at a tertiary care hospital over the study period. The mean age of the sample was 50.93 ± 16.16 years and 53.6% of the sample was male. The most common comorbidities in the patient population were hypertension (39.3%) and diabetes mellitus (25.0%). The most common indications for conducting the SBE procedure were obscure gastrointestinal bleed (39.3%), chronic diarrhea (19.7%), and unexplained anemia (16.4%). Other indications included enteric thickening or inflammatory changes on imaging, space occupying lesions, persistent vomiting, weight loss, and malabsorption syndromes. Most of the procedures were conducted in the endoscopy suite while 9.8% (n = 6) required the operation room due to patient comorbidities or being in conjunction with a surgical procedure. The majority of the procedures were carried under monitored anesthesia care (93.4%) while the rest were done under general anesthesia. Most procedures were diagnostic (91.8%) and completed without complications (95.1%). The depth of examination ranged from 95 cm to 500 cm with a mean of 282.05 ± 90.04 cm. The most common enteroscopy findings were inflammation and ulcerations (29.5%), followed by masses (19.7%) and vascular malformations (14.8%). Biopsy samples were taken in 33 of the cases and the most common biopsy finding was non-specific inflammation (63.6%). As a result of the findings, a new diagnosis was made in 47.5% of the cases and a previous one was ruled out in 24.6% of them; 65.6% of the cases had a change in management.

Research conclusions

Through our study findings, we concluded that SBE is a useful method in diagnosing small bowel problems with a good yield. It is also relatively safe and has a low risk of complications.

Research perspectives

More research needs to be conducted on the usage and yields from SBE procedures in low-middle income countries with larger samples. There also needs to be a standardized method to record the details of enteroscopy procedures.

FOOTNOTES

Author contributions: Inam M participated in the acquisition, analysis, and interpretation of the data, and assisted in manuscript writing and review; Karim MM participated in the acquisition and interpretation of the data, and assisted in manuscript writing and review; Tariq U participated in the acquisition of the data and assisted in manuscript writing and review; Ismail FW conceptualized, designed, and supervised the study, participated in the acquisition and interpretation of the data, and assisted in manuscript writing and review; all authors have read and approved the final manuscript.

Institutional review board statement: Approval was obtained for this study from the Ethical Review Committee of the Aga Khan University Hospital, Karachi, Pakistan.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrolment.

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ORIGINAL ARTICLE

Prospective Study

Role of endoscopic ultrasound in evaluation of patients with missed common bile duct stones

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Abstract

BACKGROUND

Choledocholithiasis develops in up to 20% of patients with gall bladder stones. The challenge in diagnosis usually occurs with small stones that may be missed by magnetic resonance cholangiopancreatography (MRCP). Endoscopic ultrasound (EUS) is accurate in detecting common bile duct (CBD) stones missed by MRCP, especially the small ones or those impacted at the distal CBD or the papillary region.

AIM

To evaluate the accuracy of EUS in detecting CBD stones missed by MRCP.

METHODS

Patients with an intermediate likelihood of choledocholithiasis according to ESGE guidelines and those with acute pancreatitis of undetermined cause were included. The presence of choledocholithiasis was evaluated by MRCP and EUS, and then results were confirmed by endoscopic retrograde cholangiopancreatography (ERCP). The sensitivity and specificity of EUS and MRCP were compared regarding the presence of stones, the size, and the number of detected stones.

RESULTS

Ninety out of 100 involved patients had choledocholithiasis, while ten patients were excluded as they had pancreatic or gall bladder masses during EUS examination. In choledocholithiasis patients, the mean age was 52.37 ± 14.64 years, and 52.2% were males. Most patients had biliary obstruction (74.4%), while only 23

(25.6%) patients had unexplained pancreatitis. The overall prevalence of choledocholithiasis was 83.3% by EUS, 41.1% by MRCP, and 74.4% by ERCP. Also, the number and size of CBD stones could be detected accurately in 78.2% and 75.6% by EUS and 41.1% and 70.3% by MRCP, respectively. The sensitivity of EUS was higher than that of MRCP (98.51% *vs* 55.22%), and their predictive value was statistically different ($P < 0.001$). Combination of both tools raised the sensitivity to 97.22% and specificity to 100%.

CONCLUSION

EUS could be a useful tool in assessing patients with suspected choledocholithiasis especially if combined with MRCP. However, its usefulness depends on its availability and the experience of the local centers.

Key Words: Magnetic resonance cholangiopancreatography; Endoscopic ultrasonography; Choledocholithiasis; Missed common bile duct stones

Core Tip: Still, there is a great challenge in diagnosing suspected cases of choledocholithiasis that could develop in up to 20% of patients with gall bladder stones. Endoscopic ultrasound (EUS) can easily detect small stones that magnetic resonance cholangiopancreatography (MRCP) could miss. EUS still has many diagnostic purposes with high accuracy in detecting common bile duct (CBD) stones missed by MRCP, especially the small ones or those impacted at the distal CBD or the papillary region.

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INTRODUCTION

Choledocholithiasis is considered one of the most important causes of abdominal pain in patients with gall bladder stones. It can occur in 3%-16% of patients with gall stones and can reach up to 21% in patients with gall stone pancreatitis[1,2]. Diagnosis of choledocholithiasis is not always straightforward [3]. Clinical evaluation and biochemical tests are insufficient to establish a firm diagnosis without reliable confirmatory testing, so magnetic resonance cholangiopancreatography (MRCP) is routinely used to clarify the diagnosis after ultrasound results[4]. Endoscopic retrograde cholangiopancreatography (ERCP) is now considered the gold standard for diagnosis; however, its invasive nature and complications such as pancreatitis defer its use in diagnosis as a first option[5].

Since the recommendations by the ASGE and ESGE guidelines for diagnosing patients with an intermediate likelihood of choledocholithiasis by MRCP, endoscopic ultrasound (EUS) is now widely used to assess the presence of choledocholithiasis[6,7]. Despite its overall high accuracy, the role of EUS in the diagnosis of choledocholithiasis has not been firmly established since EUS is relatively invasive compared with MRCP and computed tomography[8].

The cause of biliary obstruction is not always detected by the available non-invasive imaging modalities like MRCP and may be detected later during biliary drainage as small stones, so in our study, we evaluated the usefulness and accuracy of EUS in detecting missed stones by MRCP as a cause of biliary obstruction.

MATERIALS AND METHODS

Methodology

This observational cohort study aimed primarily to evaluate the usefulness and accuracy of EUS in detecting missed stones by MRCP as a cause of biliary obstruction.

Patients and assessments

This prospective study was conducted on 100 patients recruited from National Liver Institute and Internal Medicine Department, Kasr Al-Ainy Hospital from 2019 to 2021. We included patients with dilated CBD (diameter ranging from 6 to 10 mm), those with unexplained elevated liver enzymes, and

those with unexplained causes of acute pancreatitis. All patients with cholangitis were excluded from the study and referred for urgent ERCP drainage. Also, we excluded patients with malignant masses found by EUS and confirmed by histopathology. All included patients were above 18 years of age.

Assessment of our patients was performed by liver function tests, serum amylase, lipase, abdominal ultrasound, MRCP, and EUS. ERCP was conducted on all patients for confirmation of the findings of MRCP and EUS. MRCP was done few days before EUS, then ERCP was done later on. The EUS operator was blind to MRCP examination. We followed up with the patients for 3 mo after the procedures clinically and biochemically.

Results from MRCP and EUS were compared with those from ERCP to calculate the sensitivity and specificity of EUS and MRCP in detecting choledocholithiasis in our patients. Also, the accuracy of both MRCP and EUS in detecting the size and number of stones in CBD was evaluated.

Our institution's Research Ethical Committee approved the study, and all patients gave their informed written consent before inclusion in the study, according to the ethical guidelines of the 1975 Declaration of Helsinki.

Examination procedure

All the patients, after thorough full history taking and clinical examination, were subjected to: (1) EUS examination using a linear Echoendoscope Pentax EG3870UTK (HOYA Corporation, PENTAX Life Care Division, Showanomori Technology Center, Tokyo, Japan) connected to a Hitachi AVIUS machine (Hitachi Medical Systems, Tokyo, Japan). All examinations were performed under deep sedation with IV propofol. For EUS-FNA, we used the Cook 19G and 22G needles (Echotip; Wilson-Cook, Winston Salem, NC). Prophylactic ceftriaxone (1 g) was administrated before the procedure; and (2) ERCP examination that was performed using a side view scope Pentax ED-3490TK (HOYA Corporation, Tokyo, Japan). All examinations were performed under deep sedation with IV propofol. Prophylactic ceftriaxone (1 g) was administrated before the procedure.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software version 20.0 (Armonk, NY: IBM Corp). Qualitative data are described using numbers and percentages. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data are described using range (minimum and maximum), mean, standard deviation, median, and interquartile range. The significance of the obtained results was judged at the 5% level. The chi-square test was applied to compare categorical variables between different groups. The Fisher's exact test was used for correction for chi-square when more than 20% of the cells had an expected count of less than 5.

RESULTS

After excluding the ten patients with malignancy, the total number of male patients was 47 (52%), and that of female patients was 43 (48%), who were included till the end of the study with a mean age of 52.37 ± 14.64 years (Figure 1). The number of patients who fulfilled the criteria of an intermediate probability of biliary obstruction were 67 (74.4%), while that of patients with unexplained acute pancreatitis was 23 (25.6%). Only seven patients proved to have CBD stones, of whom all were detected by EUS, but only four were detected by MRCP. No other causes of acute pancreatitis as cystic pancreatic lesions, pancreatic divisum, or pancreatic duct stones could be detected by MRCP or EUS. Most patients had elevated liver enzymes (60%) and direct hyperbilirubinemia (81%), as shown in Table 1. Abdominal ultrasound showed that 72.2% of patients had gall bladder stones; meanwhile, only nine had a history of cholecystectomy with a mean CBD diameter of 9.13 ± 2.35 mm (Figure 2).

Choledocholithiasis was detected in 83.3% of patients by EUS, 74.4% by ERCP but only 41.1% by MRCP. EUS detected the number of stones more accurately than MRCP (95% *vs* 41%, respectively), as shown in Table 2.

Regarding the size of stones, EUS had a higher accuracy in detecting stones less than 5 mm (25 out of 53 negatives for stones by MRCP), as shown in Table 2.

EUS was statistically more accurate than MRCP in detecting stones ($P < 0.001$), especially in stones less than 5 mm (88.8% *vs* 66.6%, respectively). The sensitivity of EUS was 98.51%, while that of MRCP was only 55.5%, but the specificity of MRCP was higher than that of EUS (100% *vs* 60.87%, respectively), as shown in Table 3. The combination of EUS with MRCP showed a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy of 97.22%, 100%, 100%, 91.67%, and 97.87%, respectively (Table 4).

Indeed, there are differences in endoscopic skill between endoscopists, so we analyzed the data for expert and non-expert endoscopists (Table 5).

We found ten cases considered false negative by EUS, where six cases had gravels on EUS, three had small non-floating stones less than 5 mm, and one had a stone over the old plastic stent. Figures 3-5 show different forms of detected CBD stones from our patients.

Table 1 Biochemical data of the included patients

	n	%
Alanine transaminase, aspartate aminotransferase	Up to 33 U/L	
Normal	36	40.0
< 3 fold	44	48.9
≥ 3 fold	10	11.1
Bilirubin	Up to 1.1 mg/dL	
Normal	17	18.9
Yes	73	81.1
< 5 mg/100 mL	54	74.0
≥ 5 mg/100 mL	19	26.0
Min-Max	1.40-20.0	
mean ± SD	3.99 ± 3.30	
Median (IQR)	3.0 (2.0-5.0)	
Alkaline phosphatase	35-104 U/L	
GGT	Up to 40 U/L	
Normal	7	7.8
< 3 fold	24	26.7
≥ 3 fold	59	65.6

IQR: Interquartile range; GGT: Gamma glutamyl transpeptidase.

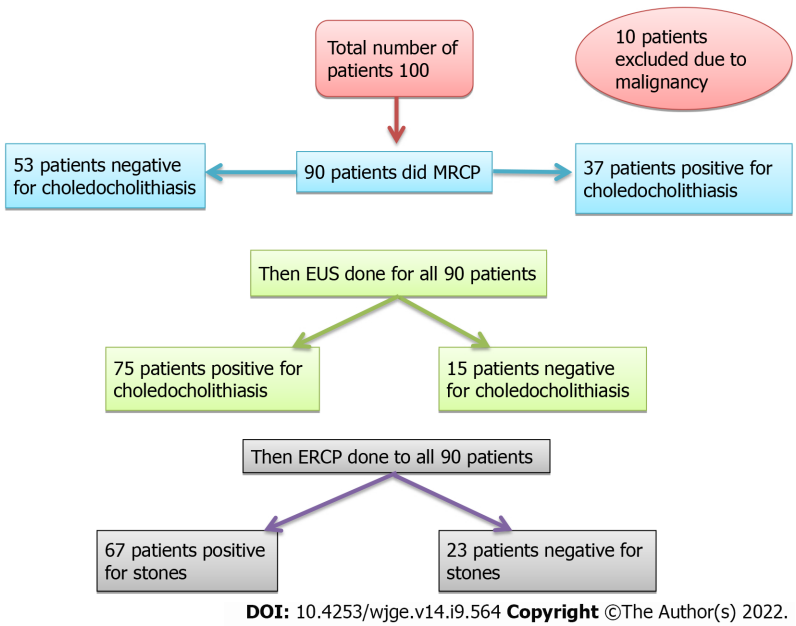

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Figure 1 Flow chart of the studied patients. MRCP: Magnetic resonance cholangiopancreatography: EUS: Endoscopic ultrasound; ERCP: Endoscopic Retrograde Cholangiopancreatography.

The ten cases with the malignant cause of biliary obstruction were detected by EUS as seven cases with pancreatic head mass, two with gall bladder carcinoma, and one with CBD mass (diagnosed as cholangiocarcinoma by further evaluation with spyglass).

Table 2 Cases of choledocholithiasis detected by endoscopic ultrasound

Common bile duct stones detected by endoscopic ultrasound	Patients (*n*)	%
Common bile duct stones detected by endoscopic ultrasound		
No	15	16.7
Yes	75	83.3
Stones (*n*)		
No stones	20	22.2
1	42	46.7
2	12	13.3
3	5	5.6
4	1	1.1
5	1	1.1
6	1	1.1
Multiple	8	8.9
Size of stones (mm)		
No stones	20	22.2
Gravels (1-2 mm)	2	2.2
3-5	25	27.8
> 5	43	47.8

Table 3 Accuracy, sensitivity, and specificity of endoscopic ultrasound and magnetic resonance cholangiopancreatography in detecting choledocholithiasis

	Endoscopic retrograde cholangiopancreatography findings				Sensitivity	Specificity	PPV	NPV	Accuracy
	No (*n* = 23)		Yes (*n* = 67)						
CBD stones detected by EUS	*n*	%	*n*	%					
No	14	60.9	1	1.5	98.51	60.87	88.0	93.33	88.89
Yes	9	39.1	66	98.5					
^{FE}P value	43.464 (< 0.001)								
MRCP stones	*n*	%	*n*	%					
No	23	100.0	30	44.8					
Yes	0	0.0	37	55.2	55.22	100.0	100.0	43.40	66.67
P value	21.569 (< 0.001)								

PPV: Positive predictive value; NPV: Negative predictive value; CBD: Common bile duct; EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography.

DISCUSSION

MRCP has been used to detect biliary obstruction in the last decade, but the cause cannot be detected in many patients[5]. The latest ASGE and ESGE guidelines recommend performing MRCP or EUS for evaluating patients with an intermediate probability of choledocholithiasis. However, it does not recommend one modality over the other[6,7]. Since the wide use of EUS, many studies have evaluated its role in detecting the cause of biliary obstruction[8]. EUS has a high accuracy in diagnosing pancreatic diseases and sampling tissues, but its role in diagnosing choledocholithiasis has not been confirmed like in pancreatic diseases[9].

Table 4 Agreement (sensitivity, specificity, and accuracy) for combined endoscopic ultrasound and magnetic resonance cholangiopancreatography

Combined EUSMRCP	ERCP findings				Sensitivity	Specificity	PPV	NPV	Accuracy
	No (n = 11)		Yes (n = 36)						
	n	%	n	%					
No	11	100.0	1	2.8	97.22	100.0	100.0	91.67	97.87
Yes	0	0.0	35	97.2					
^{FE}P value	41.887 (< 0.001)								

PPV: Positive predictive value; NPV: Negative predictive value; EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography.

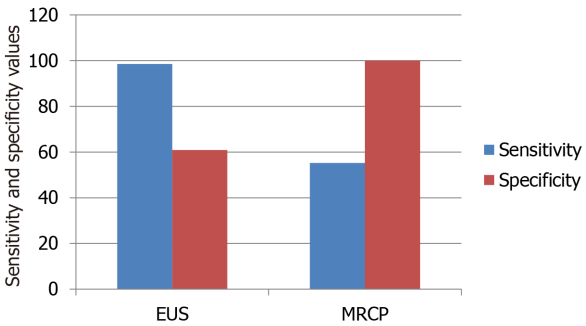

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Figure 2 Comparison of sensitivity and specificity of endoscopic ultrasound and magnetic resonance cholangiopancreatography in detecting choledocholithiasis. EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography.

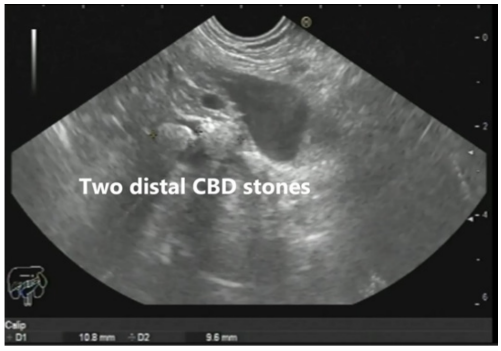

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Figure 3 Two distal common bile duct stones as seen from the gastric body. CBD: Common bile duct.

This study evaluated the accuracy of EUS in detecting CBD stones, especially those missed by MRCP in patients with an intermediated probability of CBD stones and recurrent unexplained pancreatitis. Our study included 100 patients, which is considered a large number compared to other studies like Rana *et al*[10] (40 patients) and Patel *et al*[11] (78 patients), but a small number compared to Wee *et al*[12] who included 593 patients but only 35.3% of those patients had MRCP (all our patients had MRCP).

Similar to the previously mentioned studies[10,11], we found no statistically significant variables regarding clinical and laboratory data that could predict the presence of CBD stones on EUS, MRCP, or ERCP.

In the current study, we found that EUS had a higher accuracy in detecting choledocholithiasis than MRCP (88.8% *vs* 66.6%, respectively) with a higher sensitivity (98% *vs* 55%, respectively) but lower specificity (60.8% *vs* 100%, respectively). This lower specificity of EUS might be attributed to the time gap between EUS and ERCP (passed stones), missed gravels during balloon sweeping, and false perception of air as stones in some cases. Many other studies that evaluated the diagnosis of

Table 5 Differences in endoscopic skill between expert and non-expert endoscopists

CBD stones detected by EUS	Total (*n* = 90)					Non-expert (*n* = 27)		Expert (*n* = 63)	
	n				%	*n*	%	*n*	%
No	15				16.7	11	40.7	4	6.3
Yes	75				83.3	16	59.3	59	93.7
Number									
No.	20				22.2	14	51.9	6	9.5
1	42				46.7	8	29.6	34	54.0
2	12				13.3	2	7.4	10	15.9
3	5				5.6	0	0.0	5	7.9
4	1				1.1	0	0.0	1	1.6
5	1				1.1	0	0.0	1	1.6
6	1				1.1	0	0.0	1	1.6
Multiple	8				8.9	3	11.1	5	7.9
Size (mm)									
No.	22				24.4	14	51.9	8	12.7
≤ 5	25				27.8	4	14.8	21	33.3
> 5	43				47.8	9	33.3	34	54.0
Other findings of EUS									
No	65				72.2	14	51.9	51	81.0
Yes	25				27.8	13	48.1	12	19.0
	ERCP findings				Sensitivity	Specificity	PPV	NPV	Accuracy
	No		Yes						
	n	%	*n*	%					
Total sample (*n* = 90)	*n* = 23		*n* = 67						
No	14	60.9	1	1.5					
Yes	9	39.1	66	98.5	98.51	60.87	88.0	93.33	88.89
^{FE}P value	43.464 (< 0.001)								
Non-expert (*n* = 27)	*n* = 13		*n* = 14						
No	10	76.9	1	7.1					
Yes	3	23.1	13	92.9	92.86	76.92	81.25	90.91	85.19
^{FE}P value	13.595 (< 0.001)								
Expert (*n* = 63)	*n* = 10		*n* = 53						
No	4	40.0	0	0.0					
Yes	6	60.0	53	100.0	100.0	40.0	89.83	100.0	90.48
^{FE}P value	22.637 (< 0.001)								

PPV: Positive predictive value; NPV: Negative predictive value; EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography.

choledocholithiasis by EUS showed variable results regarding sensitivities and specificities. For example, Jagtap *et al*[13] showed that the sensitivities of both EUS and MRCP were similarly high (92%-98%). Also, Patel *et al*[11] showed that the sensitivity and specificity of EUS were 93% and 97.3%, respectively, but most included patients had a high probability of choledocholithiasis. Wee *et al*[12] reported sensitivities from 85% to 100% for EUS and 73% to 99% for MRCP. In a meta-analysis of five head-to-head studies comparing EUS to MRCP for choledocholithiasis, the pooled sensitivity and

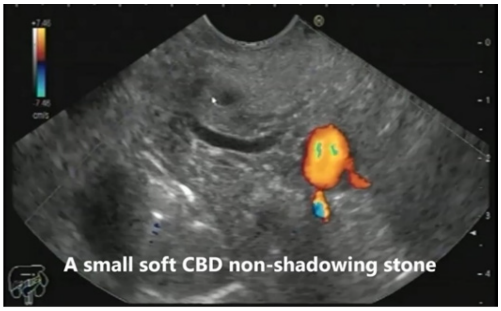

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Figure 4 A small soft non-shadowing common bile duct stone as seen from the bulb of the duodenum. CBD: Common bile duct.

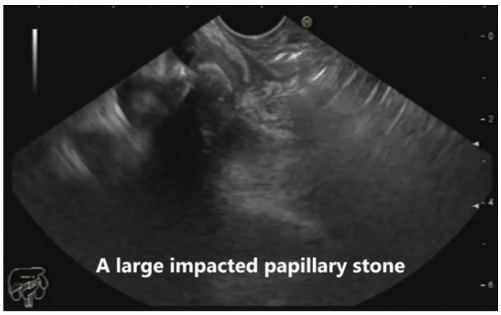

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Figure 5 An impacted stone in the region of the major papilla as seen in the mid-second part of the duodenum.

specificity of EUS were 97% and 90%, respectively, *vs* 87% and 92% for MRCP, respectively[14].

Also, de Lédinghen *et al*[15] reported a good sensitivity (100%) but low specificity (62%) for MRCP in diagnosing choledocholithiasis. Meanwhile, Materne *et al*[16] showed a 91% sensitivity and 94% specificity for MRCP, close to the values for EUS. The study conducted by Scheiman *et al*[17] reported significantly better results with EUS (sensitivity, 95%; specificity, 80%) than with MRCP (sensitivity, 40%; specificity, 96%) in diagnosing choledocholithiasis.

Another study compared the accuracy of EUS with ERCP in detecting choledocholithiasis and showed that EUS had a sensitivity of 100% and specificity of 94.7%.

One of the reasons for missed stones by MRCP that were detected by EUS was non-floating stones at the papillary region or distal CBD, as this is considered one of the pitfalls in MRCP interpretation, as mentioned by Irie *et al*[18]. Another reason was the stones with a diameter less than 5 mm (25 cases detected by EUS *vs* only 10 by MRCP), which suggests the accuracy of EUS in detecting small stones [19]. Also, EUS was superior to MRCP in detecting the number of stones inside the CBD (70 cases by EUS *vs* only 26 by MRCP), which is contradictory to the study of Aubé *et al*[20] that found no significant difference between the two modalities (MRCP detected four of six cases while EUS detected five of six cases).

Many studies comparing EUS and MRCP in idiopathic acute pancreatitis have shown that EUS has higher diagnostic yields than MRCP[21]. In this context, EUS should be considered the first choice in diagnosing idiopathic acute pancreatitis[22]. Biliary diseases such as cholelithiasis, choledocholithiasis, microlithiasis, and biliary sludge are the leading cause of idiopathic acute pancreatitis[23].

In our study, cases with unexplained pancreatitis were evaluated by EUS and MRCP, which showed that EUS was more sensitive in detecting stones than MRCP (90% *vs* 78%, respectively), as only seven patients proved to have CBD stones, of whom all were detected by EUS but only four were detected by MRCP[23]. Meanwhile, no other causes of acute pancreatitis as cystic pancreatic lesions, pancreatic divisum, or pancreatic duct stones could be detected by MRCP or EUS. And this finding is in agreement with Akkuzu *et al*[24], who reported a sensitivity of EUS and MRCP in evaluating acute pancreatitis of 89.65% and 72.4%, respectively.

Combining EUS with MRCP is very valuable in diagnosis of missed CBD stones than each one alone. In our study, the combination of the two tools raised the sensitivity, specificity, PPV, NPV, and overall accuracy into 97.22, 100, 100, 91.67, and 97.87, respectively.

The main limitation in our study was the financial cost of doing EUS, ERCP, and MRCP for all of the included patients. The second limitation was that we considered ERCP as the gold standard in detecting CBD stones. Although it is an accurate modality for detecting CBD stones, some false-negative cases may occur. Small stones may be missed if the CBD is under- or over-filling with contrast. Minute stones

or gravels may be missed during balloon sweeping. Also, in some cases, there was a time gap between ERCP and EUS that might give a chance of passage of small stones out of the CBD that could give false-positive results on EUS.

CONCLUSION

Our study showed that EUS and MRCP are not equal tools in diagnosing choledocholithiasis in patients with an intermediate probability of choledocholithiasis. EUS is more accurate than MRCP in detecting non-floating stones in the papillary region and small stones, especially those less than 5 mm, and defining the size and number of stones. Furthermore, combining EUS with MRCP proved to be very valuable in accurate diagnosis of patients with an intermediate probability of choledocholithiasis.

EUS could be a good first option for evaluating patients with an intermediate probability of choledocholithiasis when it is available with good experience.

Combining EUS with MRCP is recommended for accurate evaluation of patients with an intermediate probability of choledocholithiasis if both are available.

ARTICLE HIGHLIGHTS

Research background

Choledocholithiasis develops in up to 20% of patients with gall bladder stones. The challenge in diagnosis usually occurs with small stones that may be missed by magnetic resonance cholangiopancreatography (MRCP). Endoscopic ultrasound (EUS) is accurate in detecting common bile duct (CBD) stones missed by MRCP, especially the small ones or those impacted at the distal CBD or the papillary region.

Research motivation

Still, there is a great challenge in diagnosing cases with an intermediate probability of choledocholithiasis that develop in up to 20% of patients with gall bladder stones. EUS can easily detect small stones that MRCP could miss. EUS still has many diagnostic purposes with a high accuracy in detecting CBD stones missed by MRCP, especially the small ones or those impacted at the distal CBD or the papillary region.

Research objectives

To evaluate the accuracy of EUS in detecting CBD stones missed by MRCP.

Research methods

Patients with an intermediate likelihood of choledocholithiasis according to ESGE guidelines and those with acute pancreatitis of undetermined cause were included. The presence of choledocholithiasis was evaluated by MRCP and EUS, and then results were confirmed by endoscopic retrograde cholangiopancreatography (ERCP). The sensitivity and specificity of EUS and MRCP were compared regarding the presence of stones, the size, and the number of detected stones.

Research results

Ninety out of 100 involved patients had choledocholithiasis, while ten patients were excluded as they had pancreatic or gall bladder masses during EUS examination. In choledocholithiasis patients, the mean age was 52.37 ± 14.64 years, and 52.2% were males. Most patients had biliary obstruction (74.4%), while only 23 (25.6%) patients had unexplained pancreatitis. The overall prevalence of choledocholithiasis was 83.3% by EUS, 41.1% by MRCP, and 74.4% by ERCP. Also, the number and size of CBD stones could be detected accurately in 78.2% and 75.6% by EUS and 41.1% and 70.3% by MRCP, respectively. The sensitivity of EUS was higher than that of MRCP (98.51% *vs* 55.22%), and their predictive value was statistically different ($P < 0.001$). Combination of both tools raised the sensitivity to 97.22% and specificity to 100%.

Research conclusions

EUS could be a useful tool in assessing patients with suspected choledocholithiasis especially if combined with MRCP. However, its usefulness depends on its availability and the experience of the local centers.

Research perspectives

EUS could be a good first option for evaluating patients with an intermediate probability of choledocholithiasis when it is available with good experience. Combining EUS with MRCP is recommended for

accurate evaluation of patients with an intermediate probability of choledocholithiasis if both are available.

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FOOTNOTES

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CASE REPORT

Isolated esophageal tuberculosis: A case report

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Abstract

BACKGROUND

Tuberculosis is endemic in Senegal. While its extra-pulmonary localization is rare, esophageal tuberculosis, particularly the isolated form, is exceptional. We report here a case of isolated esophageal tuberculosis in an immunocompetent patient.

CASE SUMMARY

A 58-year-old man underwent consultation for mechanical dysphagia that had developed over 3 mo with non-quantified weight loss, anorexia, and fever. Upper digestive endoscopy showed extensive ulcerated lesions, suggesting neoplasia. The diagnosis was confirmed by histopathology, which showed gigantocellular epithelioid granuloma surrounding a caseous necrosis. Thoracoabdominal computed tomography scan did not show another localization of the tuberculosis. The outcome was favorable with treatment.

CONCLUSION

Esophageal tuberculosis should be considered when dysphagia is associated with atypical ulcerated lesions of the esophageal mucosa, in an endemic area.

Key Words: Tuberculosis; Esophagus; Endoscopy; Case report

Core Tip: Isolated esophageal tuberculosis is rare. Often discovered during the exploration of dysphagia, the endoscopic aspects are not specific, and can simulate several pathologies. Biopsies can help with diagnosis by showing the granuloma to histology or by allowing molecular biology examinations. In this manuscript, we report a case of isolated esophageal tuberculosis with vast ulcers of the esophagus, which evolved without sequelae after treatment.

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INTRODUCTION

Tuberculosis is endemic in Senegal, where it constitutes a major public health problem. In 2020, 12808 new cases of tuberculosis were reported in Senegal, the majority of which were pulmonary (National Controlling Tuberculosis Program, data not published). Extrapulmonary forms of tuberculosis are frequent, whether or not they are associated with pulmonary involvement. In the digestive tract, the terminal ileum and the cecum are most often affected. Esophageal localization is rare, especially in its isolated form. We report herein a case of isolated esophageal tuberculosis in an immunocompetent patient who responded well to antibacillary treatment.

CASE PRESENTATION

Chief complaints

A 58-year-old patient was seen in our department for dysphagia that had developed over 3 mo.

History of present illness

The patient had dysphagia that had been evolving for 3 mo with non-quantified weight loss, nonselective anorexia, and nocturnal fever.

History of past illness

The patient had undergone appendectomy at 23-years-old.

Personal and family history

The patient's other personal and family histories were unremarkable.

Physical examination

The patient was in good general condition (World Health Organization performance status of 0), with a body mass index of 21.55 kg/m^2. Clinical examination was normal.

Laboratory examinations

Biological investigations (blood count, liver function tests, glycemia, renal function, and C-reactive protein) were normal. The viral serologies for hepatitis B, hepatitis C, and human immunodeficiency virus were negative.

Imaging examinations

The thoracoabdominal computed tomography (CT) scan did not show any mediastinal lymph nodes in contact with the esophagus or other foci of tuberculosis.

ENDOSCOPIC EXAMINATION

Upper gastrointestinal (GI) endoscopy showed a jagged appearance of the thoracic esophageal mucosa for about 12 cm, stopping 3 cm above the cardia, with large irregular ulcers and raised contours. Nodules were present both at the level of the ulcers and in the normal-appearing mucosa (Figure 1A). Chromoendoscopy with narrow-band imaging did not detect areas that might suggest dysplasia or carcinoma (Figure 1B).

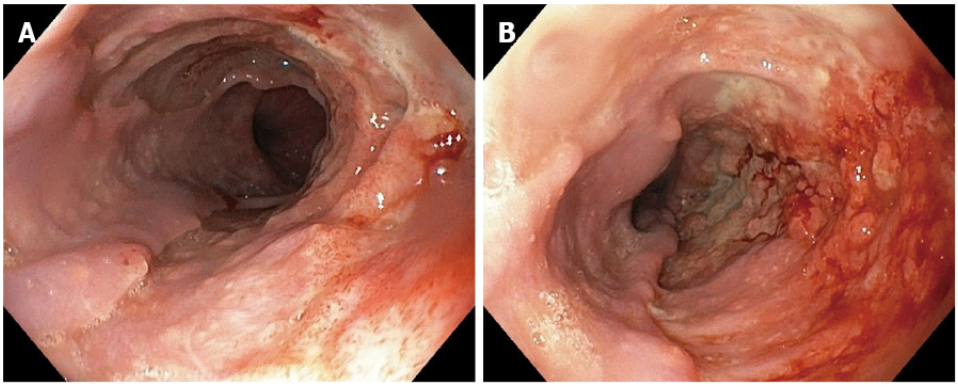

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Figure 1 Upper gastrointestinal endoscopy. A: Esophageal ulcer; B: Esophageal ulcer with nodules.

ANATOMICAL PATHOLOGY

Esophageal biopsies revealed a deep loss of wall tissue, reaching the muscularis mucosa. The normal tissue was replaced by granulation tissue containing a tuberculoid granuloma with several follicles consisting of epithelioid and multinucleated Langerhans histiocytes, surrounding a caseous necrosis (Figure 2). Neither culture of tissue samples nor PCR test for *Mycobacterium tuberculosis* were performed. Sputum and gastric acid liquid after aspiration were negative for acid-fast bacilli (AFB).

FINAL DIAGNOSIS

Isolated esophageal tuberculosis.

TREATMENT

An antituberculosis treatment was initiated [rifampicin, isoniazid, ethambutol, and pyrazinamide (RHEZ) and administered for 2 mo, and with rifampicin and isoniazid (RH) for 4 mo]. The patient showed good tolerance.

OUTCOME AND FOLLOW-UP

The patient's outcome was favorable, with a clear improvement of dysphagia after 15 d of treatment, which disappeared after 5 wk. Upper digestive endoscopy after 4 mo of treatment showed a normal esophageal mucosa. Six months after stopping the treatment, the patient was well, had regained weight, and did not complain of dysphagia.

DISCUSSION

Described for the first time in 1837 by Denonvilliers during an autopsy, infectious esophagitis due to tuberculosis is rare, even in countries with high tuberculosis endemicity. The esophageal localization represents 0.2%-1% of tuberculosis cases of the GI tract[1,2]. This low incidence can be explained by several mechanisms that allow the esophagus to fight infection, in particular, peristaltic movements leading to emptying of the contents into the stomach, and the presence of mucus and saliva lining the mucosa and its squamous epithelium[1]. These mechanisms provide a barrier against primary contamination caused by the ingestion of food or saliva containing germs such as *M. tuberculosis*. However, secondary contamination by contact with neighboring organs, especially in cases of tuberculosis in paraesophageal lymph nodes, is possible[3]. Blood-borne contamination is rare.

The most common symptom during esophageal tuberculosis is dysphagia (90% of cases), which was the main sign in our patient. Odynophagia, pyrosis, and chest pain may also be present[4]. The occurrence of coughing at mealtime should raise suspicion of an esotracheal or esophageal-mediastinal fistula, which is present in 13%-50% of cases[5]. The presence of hematemesis can also provide further evidence of a fistula[6].

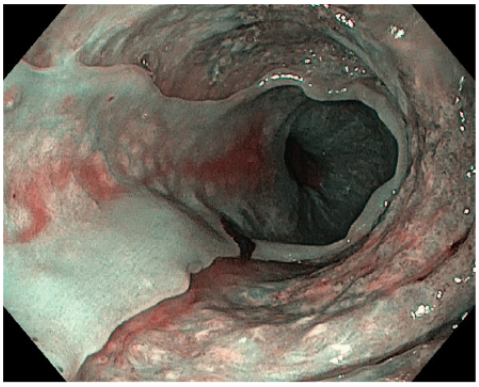

Figure 2 Esophageal biopsies. Esophageal ulcer detected in narrow band imaging.

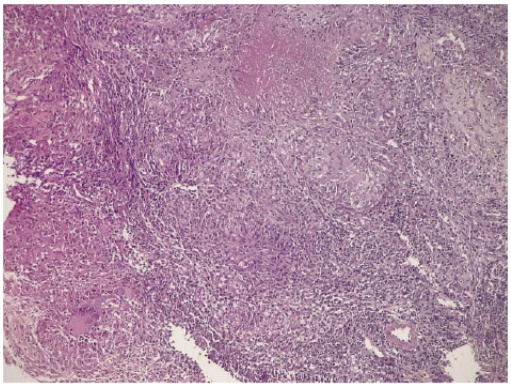

Figure 3 Granuloma with caseous necrosis (hematoxylin-eosin: 10 ×).

The endoscopic appearance of esophageal tuberculosis is variable and nonspecific. In our patient, the lesion was located in the lower two-thirds of the esophagus and consisted of a large ulcer with raised contours, associated with micronodules. The esophagus can be affected throughout its length, although the lesion is most often located in the middle third[3,7,8], because of the extensive lymphoid tissue in this region. Endoscopy may show an ulcer of variable size, superficial with regular contours or irregular and infiltrative simulating neoplasia, or show a more or less ulcerated budding aspect of the mucosa[3, 9]. An extrinsic compression aspect with a mucosa of normal appearance can also be found[8]. Endoscopic ultrasound can be helpful for diagnosis, allow analysis of the thick esophageal wall, and guide biopsies[7]. It also allows for exploration of the mediastinum and performance of fine-needle biopsy of potentially involved lymph nodes[7]. Thoracic CT scan often shows a thickening of the eso-phageal wall and allows for searching of adjacent lymph nodes, pulmonary location, or esotracheal or esophago-mediastinal fistulas.

Histology can help in the diagnosis of esophageal tuberculosis. Mucosal biopsies during upper GI endoscopy can show the presence of a tuberculous granuloma or AFB in about 50% of cases[10,11], but sometimes neither of these lesions is found[12]. In our patient, an epithelioid gigantocellular granuloma with caseous necrosis was present on histology (Figure 3), confirming the diagnosis of esophageal tuberculosis. To improve diagnostic success, deep biopsy samples should be taken from ulcerated areas, as granulomas are most often found in the submucosa[1,8,11]. If endoscopic biopsies are not contributive, deep esophageal biopsy or fine-needle aspiration of a satellite lymph node, guided by endoscopic ultrasound, make it possible to find an epithelioid granuloma on histology (reportedly in 94.7% to 100% of cases, with caseous necrosis and/or AFB present in 55% to 75% of those cases)[7,11]. Histological samples are also used for PCR or culturing methods to identify *M. tuberculosis*. If an epithelioid granuloma without caseous necrosis is present, a differential diagnosis with sarcoidosis, Crohn's disease, or a carcinoma must be considered.

The treatment of esophageal tuberculosis is essentially medical, according to the standard protocol (rifampicin, isoniazid, ethambutol, and pyrazinamide daily for 2 mo, followed by rifampicin and isoniazid daily for 4 mo) for at least 6 mo. However, the optimal duration is not clinically established. In the case of fistula, clips are the reference treatment for lesion closure[11,13]. The outcome during treatment for esophageal tuberculosis is favorable and without sequelae in almost all cases[3,7,8,11]. In

our patient, no sequelae were noted during the follow-up. Upper digestive endoscopy, 4 mo after the beginning of treatment, was normal. The patient had no complaints at 6 mo after the end of treatment.

CONCLUSION

Esophageal tuberculosis is a rare cause of infectious esophagitis, even in a country where tuberculosis is endemic. Nevertheless, esophageal tuberculosis should be considered when dysphagia is associated with atypical ulcerated lesions of the esophageal mucosa. The presence of gigantocellular epithelioid granulomas on esophageal biopsies confirms the diagnosis. The patient's outcome is generally favorable after antibacillary treatment, as illustrated by our observation.

FOOTNOTES

Author contributions: Diallo I performed the upper digestive endoscopy, followed up with the patient, and wrote the manuscript; Touré O, Sow A, and Ndiaye B contributed to collecting the patient's clinical data, and participated in the follow-up; Sarr ES and Dial CM conducted the anatomopathological examinations; Diawara PS conducted the biological tests; Mbengue A performed the radiological examinations; Fall F supervised the manuscript; all authors have read and approved the final manuscript.

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The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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REVIEW

Endoscopic palliation of malignant biliary obstruction

Andrew Canakis, Michel Kahaleh

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Abstract

Malignant biliary obstruction often presents with challenges requiring the endoscopist to assess the location of the lesion, the staging of the disease, the eventual resectability and patient preferences in term of biliary decompression. This review will focus on the different modalities available in order to offer the most appropriate palliation, such as conventional endoscopic retrograde cholangiopancreatography, endoscopic ultrasound guided biliary drainage as well as ablative therapies including photodynamic therapy or radiofrequency ablation.

Key Words: Biliary obstruction; Endoscopic retrograde cholangiopancreatography; Endoscopic ultrasonography; Stenting; Ablation therapy

Core Tip: Endoscopic palliation of malignant biliary obstruction can often be challenging. Endoscopic retrograde cholangiopancreatography remains the gold standard for biliary decompression. Its widespread use and high success rate, especially in expert hands, makes it an effective modality for biliary decompression. Yet, recent advances in endoscopic ultrasound guided biliary drainage have emerged from a rescue therapy to a reliable tool with high technical and clinical success rates with moderate adverse event rates. Growing evidence suggest that this can be considered as a first line option in the future. Lastly, photodynamic therapy and radiofrequency ablation of the bile duct can also optimize stent patency, palliate symptoms and prolong survival. While there are limited head to head studies, radiofrequency ablation may be a more cost effective option with lower adverse events.

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INTRODUCTION

Palliation of unresectable malignant biliary obstruction is recommended to achieve biliary decompression and allow for symptomatic relief (*i.e.*, jaundice and pruritis). Minimally invasive endoscopic biliary drainage techniques have garnered significant attention as an effective patient friendly treatment option that can improve one's quality of life when comparing it to the more invasive nature of surgery and/or percutaneous transhepatic biliary drainage (PTBD) approaches. At the present, endoscopic retrograde cholangiopancreatography (ERCP) serves as the cornerstone of biliary decompression. However, in instances of failed or inaccessible cannulation endoscopic ultrasound guided biliary drainage techniques have emerged as second line options with comparable clinical outcomes. Furthermore, localized endobiliary ablative tools *via* photodynamic therapy and radiofrequency ablation have proven to be supplementary methods to palliate symptoms and optimize stent patency. As such this state-of-the-art review will shed light on palliative endoscopic modalities for the effective management of biliary drainage.

CONVENTIONAL ERCP

Malignant biliary obstruction can be categorized as a distal or hilar obstruction. This distinction is important as management options and outcomes differ. As such, the following two sections are subdivided to describe the ERCP approach in draining malignant distal biliary obstruction (MDBO) and malignant hilar biliary obstruction.

MDBO

MDBO represents a wide clinicopathologic spectrum of intrinsic and extrinsic bile duct compression arising within the pancreaticobiliary system. The most common etiologies are pancreatic adenocarcinoma and cholangiocarcinoma; in fact, up to 70% of patients with pancreatic cancer present with distal biliary obstruction[1,2]. Since the majority of patients are diagnosed at advance stages, management *via* palliative endoscopic decompression is increasingly encountered.

ERCP with transpapillary stenting is the gold standard for decompressing unresectable MDBO with a success rate of 90%-95%[3,4]. Palliative endoscopic biliary drainage is indicated as a means to treat cholangitis while providing symptomatic relief with improved quality of life measures[5,6]. As an established therapeutic modality for over 40 years, ERCP has emerged as a more effective and less invasive option compared to surgery and PTBD. While surgical bypass may decrease rates of recurrent jaundice, it is associated with a significant morbidity and mortality[2,7,8]. A meta-analysis of five randomized controlled trials (RCT) (379 patients) found that post-operative complications and 30 d mortality (16.3% *vs* 9.6%) were higher in surgical cohort[8]. In general many of these patients are poor operative candidates, whereby complications associated with surgical intervention can delay palliative chemotherapy options as well. Similarly, ERCP is often preferred over PTBD due to lower rates of adverse events, fewer re-interventions, decreased costs, shorter duration of hospital stay, and the lack of an external drain needed[4,6,9]. A large national database comparing 7445 ERCPs *vs* 1690 PTBD procedures at community and tertiary care centers associated lower adverse events with ERCP (8.6% *vs* 12.3%, $P < 0.001$) regardless of the centers PTBD volume of expertise[9]. There is also a risk of seeding metastasis with PTBD[10]. That being said, PTBD is typically used as rescue therapy in cases of ERCP failure (which we highlight later on the EUS-BD section).

Stent selection

In order to ensure long term stent patency, placing a self-expandable metal stents (SEMS) is a well-established and cost-effective approach for patients with a life expectancy greater than 3 mo[4,11,12]. The type of stents available include covered self-expandable metal stents (CSEMS) and uncovered self-expandable metal stents (USEMS). The optimal stent type remains uncertain due to varying RCTs with mixed results (Table 1)[13-21]. A recent meta-analysis of 11 randomized controlled trials involving 1272 patients (643 CSEMS and 629 USEMS) reported no significant difference in rates of recurrent biliary obstruction or mortality[22]. While there was a 32% risk reduction for stent failure and mortality favoring CSEMS, this possibly benefit was offset but higher rates of sludge formation and stent migration[22]. Another meta-analysis of 9 RCTs (1061 patients) found no difference in length of stent patency[23]. In terms of adverse events (including pancreatitis and cholecystitis), there appears to be no

Table 1 Covered versus uncovered self-expandable metal stents in malignant distal biliary obstruction

Ref.	Study design; country	Total number subjects	Number of SEMS Placed, CSEMS *vs* USEMS	Recurrent biliary obstruction; CSEMS *vs*USEMS, *n* (%)	Stent patency CSEMS *vs* USEMS, d	Procedure related adverse events, CSEMS *vs*USEMS, % (*n* = #)
Sakai *et al* [13], 2021	Multicenter randomized control trial; Japan	92	44 *vs* 48	10 (22.7%) *vs* 21 (43.8%), *P* = 0.0467	455 *vs* 301, *P* = 0.0112	6.8% (2 cholangitis, 1 cholecystitis) *vs* 8.3% (2 pancreatitis, 2 cholangitis), *P* = 0.549
Conio *et al* [14], 2018	Multicenter randomized control trial; Italy	158	78 *vs* 80	12 (16.7%) *vs* 10 (13.2%), *P* = 0.65	240 *vs* 541, *P* = 0.031	18% (6 cholangitis, 2 cholecystitis, 5 migrations) *vs* 7.9% (6 cholangitis), *P* = 0.061
Yang *et al* [15], 2015	Single center randomized control trial; South Korea	103	51 *vs* 52	17 (33.3%) *vs* 15 (28.8%), *P* = 0.623	395 *vs* 365, *P* = 0.467	17.6% (5 cholecystitis, 3 pancreatitis, 1 cholangitis) *vs* 9.6% (3 cholecystitis, 2 cholangitis), *P* = 0.378
Lee *et al* [16], 2013	Single center randomized control trial; South Korea	40	20 *vs* 20	10 (50%) *vs* 4 (20%), *P* = 0.047	207 *vs* 413, *P* = 0.041	5% (1 cholecystitis) *vs* 0%, NS
Lee *et al* [17], 2014	Retrospective, single center; USA	749	171 *vs* 578	33 (19%) *vs* 123 (21%), *P* < 0.001	468 *vs* 799, *P* = 0.61	8.2% (10 pancreatitis, 4 cholangitis) *vs* 6.4% (6 pancreatitis, 3 cholecystitis, 28 cholangitis), *P* = 0.20
Kitano *et al* [18], 2013	Multicenter randomized control trial; Japan	120	60 *vs* 60	14 (23%) *vs* 22 (36%), *P* = 0.08	583 *vs* 314, *P* = 0.019	3.3% (1 pancreatitis, 1 cholecystitis) *vs* 3.3% (2 cholecystitis), NS
Telford *et al*[19], 2010	Multicenter randomized control trial; Canada	129	68 *vs* 61	20 (29%) *vs* 11 (18%), NS	357 *vs* 711, *P* = 0.530	4.4% (3 cholecystitis) *vs* 6.6% (3 cholecystitis, 1 pancreatitis), *P* = 0.046
Kullman *et al*[20], 2010	Multicenter randomized control trial; Sweden	379	188 *vs* 191	47 (25%) *vs* 45 (24%), *P* > 0.50	154 *vs* 199, *P* = 0.326	7.5% (2 cholecystitis,3 pancreatitis, 8 cholangitis, 1 perforation) *vs* 10.5% (2 cholecystitis,4 pancreatitis, 12 cholangitis, 1 perforation, 1 hemorrhage), *P* = 0.370
Isayama *et al*[21], 2004	Single center randomized control trial; Japan	112	57 *vs* 55	8 (14%) *vs* 21 (38.2%), *P* < 0.001	304 *vs* 161, *P* < 0.05	12.3% (5 pancreatitis, 2 cholecystitis) *vs* 5.5% (1 pancreatitis, 2 hemorrhage), NS

NS: Not significant; USA: United States.

major differences based on stent type[23,24].

To combat tumor ingrowth and prolong stent patency, paclitaxel-incorporated drug eluting metal stents have been developed in South Korea. The stent is coated with membrane layers of polytetrafluoroethylene to prevent bile acid degradation and sodium caprate to enhance paclitaxel delivery[25]. A meta-analysis of 5 studies comparing drug eluting stents (197 patients) to SEMS (151 patients) reported a pooled stent patency of 168 d and 149 d, respectively[26]. There were no major differences in rates of cholangitis (17% *vs* 15%) or cholecystitis (6.5% *vs* 5.0%). Further studies are needed to determine if these drugs eluting stents can alter the management of MDBO. None of those stents have received FDA clearance so far.

Malignant hilar lesions

Malignant hilar obstruction poses its own set of unique challenges, especially since the endoscopic intervention is often technically challenging. In a large study analyzing 59437 ERCPs, successful outcomes and reduced adverse events were associated with high volume endoscopists and centers[27]. This highlights the importance of managing these patients in a high volume multidisciplinary center, as technical failure can significantly shorten the median length of survival compared to successful biliary drainage (8.7 mo *vs* 1.8 mo, *P* < 0.001) in type III and IV hilar cholangiocarcinoma[28].

Malignant hilar strictures can be categorized based on their extent of hilar and/or hepatic duct involvement *via* the Bismuth-Corlette classification system[29]. Since the majority of these strictures are inoperable with varying degrees of anatomical complexity, this classification can help guide the palliative approach for biliary decompression[30]. In general Bismuth grades I/II are amenable to ERCP, however grades III/IV are typically managed by a combination of ERCP and/or PTBD[4]. Choosing between ERCP and PTBD for types III/IV was analyzed in a meta-analysis of 9 studies (*n* = 546 patients) where there was a higher success rate seen with PTBD over ERCP in types III/IV with comparable rates of adverse events and 30 d mortality, unfortunately the skillset of the endoscopists involved in that study was not provided[31]. Another study of 110 patients with inoperable Bismuth type III/IV, found

that failure of endoscopic stenting was associated with an acute angulation at the common bile duct and intrahepatic duct[32]. While pre-operative imaging may help guide an approach, PTBD can be technically challenging in the setting of liver metastases, ascites, and if intrahepatic bile duct is not fully dilated; thus, ERCP remains the preferred modality for drainage[33].

Choosing between the two modalities is based on multiple factors ranging from local expertise, risk of infection, possible seeding by PTBD, life expectancy, comorbidities and patient preference regarding an external catheter[31]. While there have been studies with mixed results favoring ERCP[34] and PTBD [35,36] the optimal stenting technique should be guided by achieving ≥ 50% of total liver volume drainage in order to relieve jaundice and reduce the risk of cholangitis[37]. Previously it was thought that draining 25% of liver volume was sufficient; however another study found that at least 50% drainage was a predictor of effective drainage and longer overall survival (199 d *vs* 59 d), especially in Bismuth type III strictures[38]. Another retrospective study of 78 patients with unresectable type II-IV hilar strictures found that effective liver volume drainage correlated with liver function: in which biliary drainage ≥ 33% can be obtained with preserved liver function and ≥ 50% with impaired liver function [39]. In addition to liver function, the anatomical difference in liver volume may also effect drainage, as the right lobe accounts for 55%-60% of volume, followed by 30%-35% in left and 10% of the caudate lobes[40,41]. Consequently, utilizing bilateral or multi-sectoral stenting is typically advised in high grade strictures based on varying anatomical involvement of disease[4].

Unilateral vs bilateral drainage

Choosing unilateral and/or bilateral stenting is typically based on the patient's presentation, degree of obstruction and local anatomy. Pre-endoscopic imaging is also imperative to understand and calculate the liver volume drainage needed. It is well established that one stent provides sufficient drainage in Bismuth I. However, for Bismuth II-IV there is no clear consensus.

A recent metanalysis of 21 studies with 1292 patients comparing both techniques noted similar rates of clinical efficacy and complications for both unilateral and bilateral drainage though there were higher rate of technical success in the unilateral group (97% *vs* 89%, $P = 0.003$)[42]. However, these results were not analyzed based on the bismuth classification or etiology of obstruction. A multitude of studies have compared unilateral *vs* bilateral drainage with similar rates of success[43-47]. One multicenter RCT of 133 patients with Bismuth grades II-IV reported no major differences in technical success, however the bilateral group had longer duration of stent patency (252 d *vs* 139 d) and fewer rates of reinterventions (42.5% *vs* 60.3%, $P = 0.049$)[43]. Similarly, a retrospective study of 141 patients found that bilateral drainage portended a longer survival advantage (255 d *vs* 80 d, $P < 0.0001$)[45]. Such advantages come at the expense of higher rates of complications and risk of death with bilateral drainage, irrespective of Bismuth grade[44].

Bilateral stenting techniques

In order to ensure adequate drainage, bilateral stenting techniques using a stent-by-stent (SBS) or stent-in-stent (SIS) have been utilized, though there is no clear consensus on what technique is superior due to limited data. Following deployment of the intrahepatic bile duct a second stent can be placed parallel using the SBS method or sequentially through the mesh within in the initial stent using the SIS approach [37]. These are technically challenging procedures that require high levels of experience with technical success rates ranging from 73% to 100%[33]. One retrospective comparing SIS ($n = 40$) to SBS ($n = 24$) reported similar rates of technical success (100% *vs* 96%), clinical success (93% *vs* 96%) and rates of recurrent biliary (48% *vs* 43%)[48]. Though there was a higher rate of post-procedural related pancreatitis exclusively seen in the SBS group[48]. At the same time another study found no significant difference in early (31.6% *vs* 22.7%) or late (36.8% *vs* 50.0%) complications for SBS *vs* SIS[49]. This was also demonstrated in a meta-analysis of 158 patients that found no significant difference in technical success, complications or stent occlusion[50]. Many centers prefer the SBS approach since deploying multiple stents is relatively easier and in cases of stent dysfunction reintervention is possible[33,51]. Reintervention with plastic stents placed inside SEMS is also possible after the SIS approach. Recently a newly designed Y-shaped bilateral endoscopic stent has been investigated, though further studies are needed to better define its role in clinical practice[52-54]. At our center we use the SBS approach preferentially.

ENDOSCOPIC ULTRASOUND GUIDED BILIARY DRAINAGE

Since its introduction in 2001, EUS-guided biliary drainage (EUS-BD) has emerged as an effective and reliable alternative for managing malignant biliary obstruction[55]. While ERCP remains the current gold standard, it is associated with a failure rate of up to 10%-especially in cases of surgically altered anatomy (SAA), tumor infiltration/obstruction, periampullary diverticulum, prior duodenal stenting or stenosis[4,56,57]. However, unsuccessful ERCPs may vary based on institutional experience. Two studies with extensive ERCP expertise reported unsuccessful canulation in 0.60% to 0.68% of patients [58,59]. Of note, one of those studies described 3 out of 524 failed ERCPS in native papillas with limited

instances of SAA (n = 2) or duodenal obstruction (n = 3)[59]. On the other hand a large prospective study of 4561 patients from 66 hospitals (with varying degrees of expertise) found that 17.2% of ERCPs were unsuccessful[60]. The European guidelines recommend repeating ERCP in select patients, ideally two to four days after the first ERCP, with success rates up to 82%[4].

In instances of ERCP failure where salvage therapy is needed, PTBD has conventionally been pursued; however, as mentioned above it is associated with a significant morbidity, decreased quality of life and need for re-interventions. In this context EUS-BD emerged as another less invasive option with fewer procedure related adverse events (8.80% *vs* 31.22%, P = 0.022) and re-intervention rates (0.34 *vs* 0.93, P = 0.02) when compared with PTBD in a randomized open label study[61]. A meta-analysis with 483 patients confirmed these findings and found that while there was no difference in technical success, the EUS-BD group was associated with better clinical success, less reinterventions and fewer postprocedure adverse events[62].

EUS-BD is an appealing approach, though at the moment it is a specialized technique limited to a high-volume centers. In this regard understanding the associated learning curve is needed before its widespread applicability. A few studies have looked into this, and there appears to be a clear association with significantly decreased adverse events with increased operator procedural volume over time[10,63-67]. In a single center study with 215 procedures performed by one experienced endoscopist over a 6.6 year period, there was a notable decrease in adverse events as procedural volume increased each year[67]. Other studies have proposed that 33 and 100 cases were required to achieve technical proficiency and mastery, respectively[65,66].

The routes of biliary decompression can be accomplished through a rendezvous (RV), antegrade or transluminal (intra- or extrahepatic) approach[3]. The application of EUS-RV is limited to intact gastroduodenal anatomy, when conventional ERCP cannulation fails, in which a guidewire is accessed across the anastomosis in an antegrade fashion-this salvage approach is limited by a success rates of 74%-80% with a relatively high major adverse event rate of 11%[3]. Antegrade stenting has also fallen out of favor as it can be cumbersome with a limited technical success rate of 77%[3]. The puncture site (transgastric into left intrahepatic duct) allows for guidewire placement across the stricture/papilla without the need for fistula tract formation at the puncture site[68]. In instances of technical failure, antegrade stenting can be converted to transmural or PTBD[68]. Overall, direct transmural drainage is preferred *via* extrahepatic or intrahepatic approach.

Extrahepatic approach

EUS-guided choledochoduodenostomy (EUS-CDS) is a transluminal approach that creates a fistula between the duodenum and extrahepatic bile duct using a fully covered SEMS or lumen-apposing metal stents (LAMS)[68]. This biliodigestive anastomosis provides optimal palliation of MDBO; however it cannot be performed in cases of proximal obstruction or instances of gastric outlet obstruction where access to the duodenal bulb may be hindered[69]. A recent multicenter retrospective study compared EUS-CDS (n = 28) to PTBD (n = 58) and found that EUS-CDS was associated with higher clinical success (84.6% *vs* 62.1%, P = 0.04) with significantly lower rates of reintervention (10.7% *vs* 77.6%, P < 0.001)[70]. As a clinically effective technique (up to 96.2%), EUS-CDS has emerged as reliable alternative with acceptably low adverse events (10.5%)[71].

Recent studies have increasingly been using LAMS, which may be attributing to lower rates of stent malfunction. A large multicenter cohort in the United Kingdom and Ireland found that the technical success, clinical success, adverse events and reintervention rates using LAMS were 90.8%, 94.8%, 17.5%, and 8.3%, respectively[72]. Initially, plastic stents were used when EUS-CDS was first introduced. However, CSEMS quickly replaced plastic stents as a means to reduce bile leaks and stent occlusion[3] with significantly lower rates of adverse events (13.0% *vs* 42.8%, P = 0.01) and improved stent patency when compared to plastic stents[73-75]. At the moment the use of CSEMS *vs* LAMS varies from center to center. The large, tubular and rigid shape of CSEMS can theoretically increase the risk of stent migration [3]. In this context, LAMS were designed as a short, dumbbell shaped stents wit bilateral flanged ends which provide anti-migratory properties by anchoring across non-adherent lumens[3]. Further improvements were made with the development of an electrocautery-enhanced delivery system that enables a faster single step "free-hand" puncture which has led to high rates of technical success by eliminating the need for accessory changes[76]. However, two recent studies comparing LAMS *vs* SEMS found no differences in technical and clinical success or postprocedure related adverse events[77,78].

Intrahepatic approach

In instances of proximal malignant obstruction EUS-guided hepaticogastrostomy (EUS-HGS) creates a fistulized tract between the gastric wall and left intrahepatic duct. Its technical feasibility was first introduced in 2004 and since then it has become a widely used technique[79]. The European Society of Gastrointestinal Endoscopy recommends placement of partially or fully covered SEMS for drainage of malignant obstruction[68]. HGS can be performed where there is dilation of the left intrahepatic duct with segment III being the preferred puncture site[80]. There are a few contraindications to the procedure which include gastric wall tumor infiltration, large volume ascites, and coagulopathy[80,81]. Its role in hilar obstruction is reserved for specific cases as drainage from the left intrahepatic duct does not equate to drainage of a right sided obstruction[69]. A study described access from the proximal

duodenum to right intrahepatic duct (hepaticoduodenostomy) for cases of isolated right sided obstruction (with a technical success 100% and clinical success 83%)[82], but widespread use of this technique has not been adopted due to difficulty with scope positioning and proper identification of the duct[83].

In general, this intrahepatic approach has been favored for distal malignant biliary drainage. The HGS route is associated with a lower risk of bile leakage as the localized liver parenchyma around the fistula site can provide a tamponade effect[73]. A prospective randomized trial comparing HGS (n = 24) and CDS (n = 24) in MDBO following failed ERCP reported a higher clinical success rate in the HGS group (91% *vs* 77%) at the expense of slightly more adverse event rates (20.0% *vs* 12.5%)[84]. A multitude of studies have compared CDS and HGS approaches (Table 2)[64,84-95]. A meta-analysis of 10 studies comparing HGS (n = 208) and CDS (n = 226) found no difference in technical success (94.1% *vs* 93.7%), clinical success (88.5% *vs* 84.5%), or rates of adverse events[96].

Recently, a large single center study of 215 patients (130 malignant lesions, 85 benign lesions) undergoing transhepatic biliary drainage by one endoscopist showed that the HGS approach used in up to 90% of cases was technical and clinically effective with few instances of reintervention (17.4%) needed within the malignant cohort that survived > 6 mo[67]. In this study, the endoscopist preferred HGS over CDS to decrease the risk of bleeding, stent misdeployment and potential making pancreatic surgical resection more difficult[67,97]. Of note, a study of 23 patients with concomitant duodenal and biliary obstruction undergoing single session EUS-HGS and gastrojejunostomy found that one patient with pancreatic cancer underwent successful pancreaticoduodenectomy 168 days post-biliary drainage and the fistula remained in situ with no complications[98]. On the other hand, in a large multicenter study comparing HGS (n = 24) to CDS (n = 23), the authors preferred CDS as it takes advantage of the anatomical proximity between the duodenal bulb and extrahepatic duct, by which puncture can be easier with shorter procedure times and less guidewire manipulation[85]. Another large international study of 182 patients (95 HGS, 87 CDS) suggested that CDS was associated with being 4.5 times more likely to achieve longer stent patency at the expense of higher adverse events, which may influence decisions based on patients survival[86]. In light of advancements with oncologic care, the prospect of reduced long reintervention may steer one to use CDS, especially since reintervention is easier due to shorter stent size, cannulation and steering in the duodenum[83].

While both techniques have acceptable outcomes, there is still no clear choice. Yet tailoring the technique based on anatomical features, altered anatomy, duodenal stenosis and dilated bile ducts may help endoscopists choose the right route for each patient[57,99]. A novel individualized algorithm was proposed based on patient anatomy following failed ERCP where the authors suggested using cross-sectional imaging to determine if an intrahepatic or extrahepatic approach based on the presence or absence of intra-hepatic biliary tree dilation[99]. The algorithm favored an intrahepatic approach if possible as a means to preserve anatomy. Yet, if intrahepatic dilation was technically unsuccessful, they recommended converting to an extrahepatic approach. In their prospective cohort of 52 patients, there was a technical success rate of 96% (35 intrahepatic, 17 extrahepatic).

COMPARING ERCP AND EUS-BD FOR MANAGEMENT OF MALIGNANT BILIARY OBSTRUCTION

As detailed above, ERCP remains the first choice when treating malignant biliary obstruction. Its widespread use and high success rate, especially in expert hands, makes it an effective modality for biliary decompression. The application of EUS-BD as a rescue therapy has proven to be a reliable tool with high technical and clinical success rates with moderate adverse event rates. Furthermore, instances of SAA or duodenal invasion may preclude the use of ERCP, and EUS-BD has gained momentum as the preferred therapy (as opposed to PTBD).

There is growing interest in using EUS-BD as a potential first line approach. A multicenter retrospective study comparing ERCP (n = 104) to EUS-BD (n = 104) demonstrated similar rates of technical success (94% *vs* 93%) and adverse events (8.65% *vs* 8.65%); though 4.8% of the ERCP cohort experienced post-procedural pancreatitis[100]. EUS-BD does have an added benefit of shorter procedural times with the possibility of longer stent patency by avoiding the diseased bile duct in question[3,101]. Additionally, in cases of an indwelling gastroduodenal stent, EUS-BD has been proven as a technical and clinically superior option when compared to endoscopic transpapillary stenting[102]. A recent meta-analysis of 9 studies with 634 patients found no significant differences between technical and clinical success, though the EUS-BD cohort had fewer rates of reintervention[103].

ABLATION THERAPY OF THE BILE DUCT

The goals of palliative biliary drainage aim to improve obstructive symptoms and quality of life. Yet endoscopic biliary decompression may only provide temporary relief; hence, the ability to provide

Table 2 Comparative studies of endoscopic ultrasound guided hepaticogastrostomy and choledochoduodenostomy

Ref.	Study design, Country	Number of HGS *vs* CDS	Technical success CDS *vs* HGS, %	Clinical success HGS *vs* CDS, %	Adverse events, HGS *vs* CDS, %
Tyberg *et al*[86], 2022	Multicenter,International	95 *vs* 87	92% *vs* 92%, NS	86% *vs* 100%, NS	21% *vs* 26%, $P = 0.17$
Minaga *et al*[85], 2019	Multicenter, Japan	24 *vs* 23	87.5% *vs* 82.6%, $P = 0.028$	100% *vs* 94.7%, $P = 0.0475$	28.6% *vs* 21%, $P = 0.583$
Cho *et al*[94], 2017	Single Center, Korea	21 *vs* 33	100% *vs* 100%, NS	86% *vs* 100%, $P = 0.054$	19% *vs* 15%, NS
Amano *et al*[93], 2017	Single Center, Japan	9 *vs* 11	100% *vs* 100%, NS	100% *vs* 100%, NS	11% *vs* 18%, NS
Ogura *et al*[92], 2016	Single Center, Japan	26 *vs* 13	100% *vs* 100%	92% *vs* 100%, $P = 0.0497$	8% *vs* 46%, $P = 0.005$
Guo *et al*[91], 2016	Single Center, China	7 *vs* 14	100% *vs* 100%, NS	100% *vs* 100%, NS	14% *vs* 14%, NS
Khashab *et al*[90], 2016	Multicenter,International	61 *vs* 60	92% *vs* 93%, $P = 0.75$	82% *vs* 85%, $P = 0.64$	20% *vs* 13%, $P = 0.37$
Artifon *et al*[84], 2015	Single Center, Brazil	24 *vs* 25	96% *vs* 91%	88% *vs* 70%	20% *vs* 13%
Poincloux *et al*[64], 2015	Single Center, France	66 *vs* 26	94% *vs* 96.7%, NS	93.8% *vs* 93.1%, NS	15% *vs* 7.6%, NS
Kawakubo *et al*[88], 2014	Multicenter, Japan	20 *vs* 44	95% *vs* 95%, NS	95% *vs* 93%, NS	4% *vs* 15%, NS
Park *et al*[89], 2015	Multicenter, Korea	20 *vs* 12	100% *vs* 92%, $P > 0.99$	90% *vs* 92%, $P > 0.99$	25% *vs* 33%, $P = 0.044$
Prachayakul and Aswakul[87], 2013	Single Center, Thailand	15 *vs* 6	93% *vs* 100%, NS	93% *vs* 100%, NS	0% *vs* 33%, NS
Kim *et al*[95], 2012	Single Center, Retrospective	13 (9 CDS; 4 HGS)	100% *vs* 75%, NS	100% *vs* 50%, NS	22% *vs* 50%, NS

NS: Not significant; HGS: Hepaticogastrostomy; CDS: Choledochoduodenostomy.

supplemental biliary ablation as means to induce local tumor necrosis, optimize stent patency, palliate symptoms and possibly enhance long term survival have been investigated with photodynamic therapy (PDT) and radiofrequency ablation (RFA)[104].

Photodynamic therapy

PDT utilizes a photosensitizing agent (which is activated by laser light) to ablate tumor tissue *via* apoptosis, necrosis, and an immunomodulatory effect[105]. The porphyrin phototoxic substance is given intravenously 3-4 d prior to the procedure to allow for preferential accumulation in the malignant tissue-during this period patients are advised to stay in a darkened room to avoid an accidental inflammatory reaction in normal tissue if exposed to light[106,107]. Next a guidewire and catheter position the fiberoptic probe in the bile duct where laser light at certain wavelengths (typically 630 nm) trigger the photosensitizing agent for 750 sec to generate free oxygen radicals that destroy the tumor bed and/or stricture[106,108,109]. An added benefit to this local apoptotic and inflammatory cascade is that these light waves can refract to the proximal biliary tree which are often beyond reach of the guidewire[110]. Following PDT, a stent is often placed. This highly specialized technique is limited to a few centers.

PDT has been shown to improve overall survival, stent patency and quality of life in unresectable cholangiocarcinoma. A sentinel PDT study in 2003 prospectively randomized 20 patients to PDT plus biliary stenting and 19 with stenting alone, and found that the PDT significantly increased the median survival (493 d *vs* 98 d) while also improving quality of life and biliary drainage[111]. Similar findings of improved survival were also confirmed in another randomized trial[112]. Another retrospective comparative study of 48 patients with unresectable cholangiocarcinoma (19 PDT with stent versus 29 with biliary stent only) demonstrated a significant survival advantage (16.2 mo *vs* 7.4 mo) with only three adverse events related to skin phototoxicity that were treated with topical therapy[113]. The survival benefit of PDT plus stenting has been confirmed in three meta-analyses[114-116]. Of note, while one of these studies reported an improved survival rate favoring the PDT cohort (525 *vs* 146), the analysis was limited by its inclusion of endoscopically and percutaneous administration of PDT and/or biliary stents[116]. That being said all studies favored PDT's improved survival benefit, with a relatively low adverse event rate of 11% specific to phototoxic reactions (*i.e.*, blisters, erythema, and pruritis)[115]. In order to avoid such a reaction, it is recommended that patients avoid direct sunlight for 4-6 wk after the procedure[104].

In light of these favorable findings, additional studies have been pursued to characterize the potential benefits of stent patency and effect of combination systematic therapy. A retrospective of 33 patients with unresectable disease found that the PDT cohort ($n = 18$) had noticeable longer periods of stent patency (224 d *vs* 177 d, $P = 0.002$) by which the authors felt that PDT may induce tumor "remodeling" to lessen cholestasis and prolong biliary decompression[117]. A synergistic effect between PDT and

systematic chemotherapy has also been prospectively[118] and retrospectively confirmed to enhance overall survival[119,120]. In on such study, 96 patients with unresectable perihilar and distal CCA were stratified by treatment type where median overall survival was 20 mo, 15 mo, and 10 mo in the combination PDT plus chemotherapy (n = 36), PDT alone (n = 34), and chemotherapy alone (n = 26) groups, respectively[120].

These positive findings must also be analyzed in context of the limitations of PDT use. It is a complex and exceedingly expensive procedure that typically is only performed in highly specialized centers[2]. The phototoxic side effects may not acceptable to patients, especially since minimizing direct sunlight one month after the procedure could impair the quality of life in a patient with a potentially short life expectancy[110]. While the last author in this present review has pioneered early PDT studies, we feel that the lack of FDA approval of this therapy, in the biliary tree, has made this therapy very difficult to be offered outside of specialized centers.

Radiofrequency ablation therapy

RFA uses electromagnetic energy and high wave frequencies to deliver thermal energy to targeted tissues[121,122]. This localized thermal energy induces direct coagulative necrosis and an indirect localized inflammatory response and T-lymphocyte activation which have anti-tumor properties[110,122]. Intraductal RFA can be performed during a conventional ERCP where a RFA catheter can pass over the guidewire in order to place the bipolar probes upstream from the stricture site, whereby ablation is applied with 7-10 watts for 1-2 min bursts, along the length of the stricture[104,123]. Afterwards the bile duct is cleared with a balloon sweep to remove residual debris and necrotic tissue followed by placement of plastic or metal stent to maintain adequate drainge[104,123]. Of note, RFA can also be used with balloon enteroscopy-assisted ERCP[124] or an EUS-guided HGS approach[125,126].

The indication for endobiliary RFA is to improve stent patency and survival in cases of inoperable malignant strictures[106,123]. In 2011, a prospective pilot study analyzed the utility of RFA in 21 patients with unresectable malignant biliary obstruction, and found that biliary patency was maintained by 20 and 16 patients at 30 and 90 d, respectively with no adverse events related to RFA[127]. However, a subsequent single center retrospective study of 66 patients demonstrated no added benefit in prolonged stent patency when comparing metal stenting with RFA to stenting alone[128]. Of note, this study did not differentiate their findings based on the stent used. Another study found a significant improvement and durability of stricture diameter using plastic (n = 6) and metal stents (n = 14)[129]. As such, analyzing endobiliary RFA according to the type of stent used may allow for a better interpretation of stent patency; as etiology of recurrent biliary obstruction varies from sludge formation, migration and tumor ingrowth for plastic stents, covered SEMS and uncovered SEMS, respectively[123,130].

Plastic stents are often used if repeated RFA sessions are planned. Two recent RCTs have examined the stent patency of RFA and plastic stents with conflicting results[131,132]. In one study, of 65 patients (32 RFA plus plastic stent, 33 plastic stent alone), stent patency was significantly longer (6.8 mo *vs* 3.4 mo) with a higher survival time (13.2 mo *vs* 8.3 mo) favoring the RFA and plastic stent arm[133]. While the other RCT also reported a higher survival time (14.3 mo *vs* 9.2 mo) there was no significant difference in stent patency or jaundice control in either group[134]. One possible reason for the discrepancy is that in the first RCT by Yang *et al*[133] patients underwent stent exchange every 3 mo, while the study by Gao *et al*[134] only performed a stent exchange as clinical indicated. In our practice we offer systematic stents revision at three months interval.

The use of SEMS is largely depending on the patient's life expectancy and unresectability. Both uncovered and covered SEMS have been investigated with mixed results[131,132,135]. A retrospective [131] and RCT[132] examining USEMS, found no significant differences in stent patency. Meanwhile, a single center retrospective study using UCSEMS and CSEMS in a cohort of 31 patients favored the use of either stent with RFA with prolonged stent patency (220.0 d *vs* 106.5 d)[135]. One meta-analysis of nine studies with 505 patients demonstrated a favorable mean stent patency of 50.6 d with improved survival in those undergoing RFA with SEMS compared to SEMS alone[136]. However, these findings should be interpreted with caution as four of these studies used a percutaneous route for RFA. In this context, another meta-analysis of 263 patients undergoing endoscopic RFA showed that strictures improved by 3.5 mm when using RFA with a median stent patency of 7.6 mo[137]. Yet, the authors did not stratify their findings based on the type of stent used.

While the findings of stent patency and survival benefit are confounded by study heterogeneity and route of RFA, there is a likely benefit of stent patency and overall survival with RFA in malignant biliary obstruction. In fact a recent RCT found that a combination of oral 5-fluoouracil and RFA improved the median overall survival (16 mo *vs* 11 mo) and period of stent patency (6.6 mo *vs* 5.6 mo)[138]. With more wide spread use, developments of newly automatic temperature controlled RFA systems[139] and endoluminal devices[140] have produced favorable results pertaining to both stent patency and survival. Interestingly, RFA appears to be a relatively safe procedure with few instances of cholecystitis (10%), cholangitis (6.2%), and pancreatitis (2.1%) that did no differ significantly when compared to stenting alone[107,136].

Table 3 Comparing Photodynamic therapy to endobiliary radiofrequency ablation

Treatment type	Mechanism	Adverse events	Pros	Cons
Photodynamic therapy	Photosensitizing agent is given intravenously 3-4 d prior to accumulate in tissue; then, a fiberoptic probe is introduced to transmit laser light (approximately 630 nm)-apoptosis, necrosis, and immunomodulatory effect	Phototoxicity, erythema, pruritus, blistering, and diffuse pain	Light waves can refract to the proximal biliary tree, beyond the reach of the guidewire	Expensive; highly specialized equipment needed; decreased quality of life (avoid direct sunlight 4-6 wk after treatment); limited to high specialized centers; lack of FDA approval
Endobiliary radiofrequency ablation	High frequency electromagnetic energy-cell death *via* thermal energy, coagulative necrosis, and indirect anti-tumor lymphocyte activation	Pancreatitis, cholecystitis, cholangitis hemobilia, abdominal pain	Widely available	Lack of standardization; potentially need > 1 session; can only be performed under fluoroscopy

Only a handful of studies have directly compared RFA to PDT (Table 3). One retrospective study found no statistically significant difference in the survival benefit between RFA (n = 16) and PDT (n = 32) in their cohort of unresectable cholangiocarcinoma (9.6 mo *vs* 7.5 mo)[141]. However, the other retrospective study showed that RFA was associated with better short-term effects (*i.e.*, reduction in bilirubin with fewer unplanned stent replacements)[142]. A recent meta-analysis of 55 studies comparing PDT (n = 1149), RFA (n = 545), and stent-only strategy (n = 452) found that PDT was associated with an improved overall survival rate (11.9 mo *vs* 8.1 mo *vs* 6.7 mo, respectively) and decreased 30-d mortality (3.3% *vs* 7.0% *vs* 4.9%, respectively)[143]. Though PDT did display higher rates of cholangitis (23.4% *vs* 9.5%) and liver abscess (4.9% *vs* 2.6%) when compared to RFA. The authors felt that RFA may be favored in the setting of lower adverse events, decreased costs (Photofrin dose $37000 *vs* RFA catheter $1200) and similar lengths of stent patency (PDT 6.1 mo *vs* RFA 5.5 mo).

CONCLUSION

In conclusion, the optimal palliation of malignant obstruction remains a challenging task for endoscopists and requires a dedicated team able to offer a variety of intervention based on patient presentation, symptoms and expected survival.

FOOTNOTES

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Retrospective Study

Gastric intestinal metaplasia development in African American predominant United States population

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Abstract

BACKGROUND

Gastric cancer significantly contributes to cancer mortality globally. Gastric intestinal metaplasia (GIM) is a stage in the Correa cascade and a premalignant lesion of gastric cancer. The natural history of GIM formation and progression over time is not fully understood. Currently, there are no clear guidelines on GIM surveillance or management in the United States.

AIM

To investigate factors associated with GIM development over time in African American-predominant study population.

METHODS

This is a retrospective longitudinal study in a single tertiary hospital in Washington DC. We retrieved upper esophagogastroduodenoscopies (EGDs) with gastric biopsies from the pathology department database from January 2015 to December 2020. Patients included in the study had undergone two or more EGDs

with gastric biopsy. Patients with no GIM at baseline were followed up until they developed GIM or until the last available EGD. Exclusion criteria consisted of patients age < 18, pregnancy, previous diagnosis of gastric cancer, and missing data including pathology results or endoscopy reports. The study population was divided into two groups based on GIM status. Univariate and multivariate Cox regression was used to estimate the hazard induced by patient demographics, EGD findings, and *Helicobacter pylori* (*H. pylori*) status on the GIM status.

RESULTS

Of 2375 patients who had at least 1 EGD with gastric biopsy, 579 patients were included in the study. 138 patients developed GIM during the study follow-up period of 1087 d on average, compared to 857 d in patients without GIM ($P = 0.247$). The average age of GIM group was 64 years compared to 56 years in the non-GIM group ($P < 0.001$). In the GIM group, adding one year to the age increases the risk for GIM formation by 4% ($P < 0.001$). Over time, African Americans, Hispanic, and other ethnicities/races had an increased risk of GIM compared to Caucasians with a hazard ratio (HR) of 2.12 (1.16, 3.87), 2.79 (1.09, 7.13), and 3.19 (1.5, 6.76) respectively. No gender difference was observed between the study populations. Gastritis was associated with an increased risk for GIM development with an HR of 1.62 (1.07, 2.44). On the other hand, *H. pylori* infection did not increase the risk for GIM.

CONCLUSION

An increase in age and non-Caucasian race/ethnicity are associated with an increased risk of GIM formation. The effect of *H. pylori* on GIM is limited in low prevalence areas.

Key Words: Gastric intestinal metaplasia; Gastric cancer; *Helicobacter pylori*; Retrospective longitudinal study; Esophagogastroduodenoscopy; African American population

Core Tip: Gastric intestinal metaplasia (GIM) is a precancerous lesion, and previous literature showed a higher rate in the United States minorities. Our study highlighted the natural history of GIM over time. It was observed in the study that irrespective of being minorities, Non-Caucasian races/ethnicities have a higher risk for GIM. Gastritis and older age contribute to GIM formation. The effect of *Helicobacter pylori* infection was not significant in our population.

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INTRODUCTION

Gastric cancer is the fifth most common cancer and the third leading cause of cancer mortality worldwide[1,2]. Non-cardiac intestinal-type gastric adenocarcinoma represents the majority of cases in the United States[2]. In 2018, over 26000 new cases of gastric cancer were reported with 10600 deaths in the United States[3]; in 2020, more than 700000 deaths were reported globally[4]. The high mortality rate of gastric cancer is mostly attributed to the late presentation of the disease. In areas with a high incidence of gastric cancer, the mortality-incidence ratio is decreased by screening programs[1], while in areas with low incidence, surveillance programs for gastric premalignant lesions in high-risk individuals are likely an optimal screening strategy based on risk stratification.

The Correa cascade proposed that intestinal-type gastric adenocarcinoma is formed from normal gastric mucosa that progresses through a series of transition stages: Chronic gastritis, atrophic gastritis, gastric intestinal metaplasia (GIM), and dysplasia, which can progress to gastric adenocarcinoma[5,6]. The latter three histopathological findings are considered as gastric premalignant lesions. GIM is defined as the replacement of normal gastric epithelium with intestinal epithelium consisting of Paneth, goblet, and absorptive cells[7]. The replacement happens under chronic stressors like inflammation. The prevalence of GIM in the general United States population is estimated to be 5%-8%[7] with an 0.13%–0.25%[6,7] estimated annual risk of progression into gastric cancer and a median time to

progression of around 6 years[6].

Currently, GIM is more recognized as the best pre-malignant stage for surveillance because identifying and treating these lesions can potentially prevent further progression to gastric cancer[2,5]. Multiple international guidelines recommend surveillance for gastric pre-malignant lesions including GIM[8,9]; on the contrary, the American Gastroenterology Association (AGA) recommends against such screening guidelines for GIM with some exceptions[2]. Multiple risk factors have been identified to help guide surveillance including smoking, alcohol use, ethnicity, family history of gastric cancer, and genetic factors[10]. However, long-term effect of surveillance is not well understood in countries with a low incidence of gastric cancer due to the limitation of the available studies. Furthermore, the lack of clear guidelines for GIM medical management after diagnosis has added to the challenge[2]. Thus, we designed this retrospective longitudinal study to investigate potential risk factors involved in GIM formation from normal mucosa in an African American predominant United States population.

MATERIALS AND METHODS

Study design

This is a retrospective longitudinal study conducted at Medstar Washington Hospital Center. The study was reviewed and approved by the Medstar Health Research Institute and Georgetown University Hospital Institutional Review Board.

Study population

Patients with GIM were identified from the Pathology Department's database at Medstar Washington Hospital Center. Patients included in the study had undergone two or more esophagogastroduodenoscopies (EGDs) with gastric biopsy, with at least one EGD performed between January 2015 to December 2020. Exclusion criteria consisted of patients age < 18, pregnancy, previous diagnosis of gastric cancer, and missing data including pathology results or endoscopy reports. Patients with a baseline of no GIM were followed up longitudinally. The follow-up period ended at the event occurrence (GIM formation) or the last follow-up EGD. Based on the GIM status from the gastric biopsy at the end of the follow-up period, the study population was divided into two groups–GIM group and non-GIM group. Patients were excluded from the study if they were younger than 18 years old.

Data collection

Electronic medical records were reviewed to collect and analyze the following patient information: Demographics, medication use, EGDs findings, *Helicobacter pylori* (*H. pylori*) status, gastric biopsy reports, and laboratory findings. Patients' *H. pylori* statuses were exclusively based on biopsy testing.

Data analysis

To present the data, we used frequency with percentage for categorical variables and median with first and third quartile (IQR) for non-normal continuous variables. The D'Agostino-Pearson test was used to test normality. Chi-square test with Yate's correction or Kruskal-Wallis rank-sum test was performed to compare the difference between the groups. Kaplan-Meier estimators were calculated, and the curves were plotted to show the probability of GIM at a respective time interval after the baseline. To detect the differences in survival, we used Peto-Peto's weighted Log-rank test. Univariate and multivariate Cox proportional hazards regression model was performed to investigate how the predictors were associated with the risk of GIM over time. All unadjusted and adjusted hazard ratios with 95 percent confidence intervals were presented, along with the unadjusted *P* values. Statistical significance was set at a *P* value less than 0.05 and all statistical analyses were conducted with R software. The statistical methods of this study were reviewed by Jiling Chou from MedStar Health Research institute.

RESULTS

Overall data summary

Of 2375 patients who had at least 1 EGD with gastric biopsy during 2015 to 2020, 579 patients met our inclusion criteria. A total of 138 (23.8%) patients developed GIM during the follow-up period of 1087 days on average, compared to 857 d in patients without GIM ($P = 0.247$). The GIM group was older with an average age of 64 years compared to 56 years in the non-GIM group ($P < 0.001$). Female patients represented 60.7% (351 patients) of the total study population and there was not a significant difference between study groups ($P = 0.208$). Ethnicity was significantly different between the study groups ($P = 0.032$): African American, Caucasian, Hispanic and other ethnicities/races represented 72.9% (94 patients), 9.3% (12 patients), 5.4% (7 patients), and 12.4% (16 patients) of the GIM group respectively, compared to 71% (287 patients), 18.1% (73 patients), 2.7% (11 patients), and 8.2% (33 patients) in the non-GIM group respectively (Table 1).

Table 1 Data summary and comparison between patients with and without gastric intestinal metaplasia

Level		Baseline no GIM			
		Overall	No GIM	GIM	*P* value
		579	441	138	
Follow-up days [median (IQR)]		885.0 (257.5, 1901.5)	857.0 (259.0, 1834.0)	1087.0 (260.5, 2307.3)	0.247
Age baseline [median (IQR)]		58.0 (49.0, 67.8)	56.0 (46.8, 65.0)	64.00 (54.0, 72.0)	< 0.001
Sex (%)	Male	227 (39.3)	166 (37.7)	61 (44.2)	0.208
	Female	351 (60.7)	274 (62.3)	77 (55.8)	
Ethnicity/Race (%)	Caucasian	85 (15.9)	73 (18.1)	12 (9.3)	0.032
	AA	381 (71.5)	287 (71.0)	94 (72.9)	
	Hispanic	18 (3.4)	11 (2.7)	7 (5.4)	
	Other	49 (9.2)	33 (8.2)	16 (12.4)	
Obesity (%)	BMI < 30	261 (56.7)	191 (53.5)	70 (68.0)	0.013
	BMI > 30	199 (43.3)	166 (46.5)	33 (32.0)	
Smoking status (%)	Never	269 (54.8)	207 (55.3)	62 (53.0)	0.198
	Previous	119 (24.2)	84 (22.5)	35 (29.9)	
	Current	103 (21.0)	83 (22.2)	20 (17.1)	
Biopsy site (%)	≤ 2	227 (39.2)	190 (43.1)	37 (26.8)	0.001
	> 3	352 (60.8)	251 (56.9)	101 (73.2)	
H. pylori at Baseline (%)	No	499 (86.2)	382 (86.6)	117 (84.8)	0.686
	Yes	80 (13.8)	59 (13.4)	21 (15.2)	
H. pylori at follow-up (%)	No	536 (92.6)	413 (93.7)	123 (89.1)	0.114
	Yes	43 (7.4)	28 (6.3)	15 (10.9)	
n		80	59	21	
H. pylori at follow up with positive Baseline (%)	No	65 (81.2)	48 (81.4)	17 (81.0)	1
	Yes	15 (18.8)	11 (18.6)	4 (19.0)	
Gastritis (%)	No	209 (36.1)	180 (40.8)	29 (21.0)	< 0.001
	Yes	370 (63.9)	261 (59.2)	109 (79.0)	
Ulcer (%)	No	534 (92.2)	408 (92.5)	126 (91.3)	0.778
	Yes	45 (7.8)	33 (7.5)	12 (8.7)	
81 mg Aspirin Use at Baseline (%)	No	450 (77.7)	347 (78.7)	103 (74.6)	0.379
	Yes	129 (22.3)	94 (21.3)	35 (25.4)	
81 mg Aspirin use at follow up (%)	No	453 (78.2)	359 (81.4)	94 (68.1)	0.001
	Yes	126 (21.8)	82 (18.6)	44 (31.9)	
PPI usage at baseline (%)	No	392 (67.7)	285 (64.6)	107 (77.5)	0.006
	Yes	187 (32.3)	156 (35.4)	31 (22.5)	
PPI usage at follow up (%)	No	318 (54.9)	233 (52.8)	85 (61.6)	0.088
	Yes	261 (45.1)	208 (47.2)	53 (38.4)	
Blood type (%)	A	72 (31.2)	47 (28.7)	25 (37.3)	0.317
	B	42 (18.2)	28 (17.1)	14 (20.9)	
	O	109 (47.2)	82 (50.0)	27 (40.3)	
	AB	8 (3.5)	7 (4.3)	1 (1.5)	
Hemoglobin [median (IQR)]		11.2 (9.2, 12.8)	11.5 (9.5, 13.0)	10.5 (9.0, 12.2)	0.075

Hemoglobin Baseline [median (IQR)]	10.8 (9.2, 12.8)	11.8 (9.7, 13.1)	9.60 (8.40, 11.00)	< 0.001

GIM: Gastric intestinal metaplasia; IQR: Interquartile range; AA: African Americans; BMI: Body mass index; PPI: Proton pump inhibitors.

Regarding medication use, a higher percentage of the GIM group [44 patients (31.9%)] was using 81 mg of aspirin on follow-up, compared to 82 patients (18.6%) in the non-GIM group (P = 0.001). A lower percentage of the GIM group [31 patients (22.5 %)] was using proton pump inhibitors (PPI) at baseline compared to 156 patients (35.4%) in the non-GIM group (P = 0.006). However, aspirin use at baseline and PPI use on follow up was not significantly different between study groups.

On follow-up EGDs, gastritis was observed more in the GIM group [109 patients (79.0 %)] compared to 261 patients (59.2%) with gastritis in the non-GIM group (P < 0.001) (Table 1).

H. pylori was positive in the baseline biopsies of 80 patients (13.2%), compared to those of 43 patients (7.4 %) on follow-up. Of this *H. pylori* positive group, 15 patients had positive *H. pylori* at both the baseline and follow-up, but this persistent *H. pylori* infection was not different between the two study groups. A detailed summary of the data is presented in Table 1.

Risk of GIM over time

In a group of patients with no GIM at baseline, adding one year in age increases the risk of GIM by 4% over time with a P value < 0.001. In comparison to the age group of 45 years or younger, patients have a hazard ratio (HR) of 2.13 (P = 0.028), 2.09 (P = 0.029), and 4.03 (P < 0.001) for age groups 46-55, 56-64, and ≥ 65 years respectively. Over time, African Americans, Hispanics, and other ethnicities/races had an increased risk of GIM compared to Caucasians with an HR of 2.12 (1.16, 3.87), 2.79 (1.09, 7.13), and 3.19 (1.5, 6.76) respectively. Gastritis on follow-up biopsy was associated with a higher risk of GIM with an HR of 1.62 (1.07, 2.44) (P = 0.022), while 81 mg aspirin use increased the risk of GIM by 49% (P = 0.031). Obesity at baseline had a 42% less risk of GIM (P = 0.010). Using the *H. pylori*-negative group at baseline and follow-up as a reference group, *H. pylori* infection at baseline or follow-up, as well as the persistence of *H. pylori* infection did not have significant effects on GIM risk over time. Subgroup analysis of patients with *H. pylori* present at baseline shows no major difference from the main study analysis (Table 2).

On multivariate Cox regression analysis, the age ≥ 65 group was continuously associated with a higher risk of GIM with an HR of 3.01 (P = 0.014). African Americans and other ethnicities have a higher risk of GIM with an HR of 3.4 (P = 0.026) and 7.46 (P = 0.001) when compared to Caucasians respectively. Hispanic, other age groups, gastritis, *H. pylori* status, and smoking status did not reach the level of statistical significance on multivariate analysis (Table 3).

We calculated the Kaplan-Meier survival estimate for GIM development over 12 years. The population at risk is limited by the available follow-up EGD and censored observations. At the 12 years follow-up, 26 patients were at GIM risk (Figure 1A). Close to 50% of the population at risk developed GIM during 12 years of follow-up. A 12 years survival Curve was done to present the survival probability of developing GIM based on ethnicity, age group, and gastritis status (Figure 1B-D). We observed a significant difference in the GIM development over 12 years based on gastritis status (P = 0.023), age group (P < 0.0001), and ethnicity (P = 0.023).

DISCUSSION

GIM is a recognized gastric pre-malignant lesion with an increased risk for developing gastric cancer. The risk factors for GIM formation and evolution are significant clinical interest and thus currently under active investigation since these factors will likely help design optimal surveillance programs and management of GIM after diagnosis. Our study showed that the GIM group was older compared to the non-GIM group (Table 1). In multiple studies including ours, more advanced age was associated with an increased risk of GIM formation, progression, and gastric cancer development, which could be attributable to prolonged exposure of gastric mucosa to mutagenic factors and inflammation[1,4,11]. The average age at GIM diagnosis in low gastric cancer incident countries was 60 to 67 years, comparable to the average age of 64 in our GIM group (Table 1)[1,11,12]. A one-year increase in age was associated with a 4% increase in GIM risk in our population. Age groups of 45-54, 55-64, and > 65 were associated with an increased risk for GIM development compared to the < 45 age group (Table 2). The age group > 65 had the highest HR, and it was the only age group associated with an increased risk of GIM formation on multivariate analysis (Table 3). However, a study in China found that age > 45 is associated with GIM progression[13]. After five years of follow-up, around 50% of patients in group > 65 develop GIM, compared to 10% in < 45 age group (Figure 1C). These results suggest that an age close to 65 may be a good threshold for screening for GIM.

Although gastric cancer is known to be more common in males[14], GIM has equally affected both genders in our study and others[1,4]. In contrast, a cohort study in Puerto Rico showed a greater

Table 2 Univariate Cox proportional hazards regression model results for gastric intestinal metaplasia formation over time

Predictor	GIM	
	HR (95%CI)	*P* value
Age	1.04 (1.02, 1.05)	< 0.001
Age (ref: ≤ 45)		
46-55	2.13 (1.08, 4.19)	0.028
56-65	2.09 (1.08, 4.03)	0.029
> 65	4.03 (2.17, 7.48)	< 0.001
Female	0.81 (0.58, 1.14)	0.229
Race/Ethnicity (ref: Caucasians)		
African American	2.12 (1.16, 3.87)	0.015
Hispanic	2.79 (1.09, 7.13)	0.032
Other	3.19 (1.50, 6.76)	0.003
Obesity (BMI > 30)	0.58 (0.38, 0.88)	0.010
Gastritis	1.62 (1.07, 2.44)	0.022
***H. pylori* (ref: Baseline: Neg, follow-up: Neg)**		
Baseline: Neg, follow-up: Pos	0.88 (0.45, 1.7)	0.695
Baseline: Pos, follow-up: Neg	1.16 (0.7, 1.94)	0.563
Baseline: Pos, follow-up: Pos	1.02 (0.37, 2.8)	0.966
PPI Usage at follow-up	0.81 (0.57, 1.14)	0.225
PPI Usage Baseline	0.80 (0.54, 1.20)	0.280
Aspirin Use at follow-up (81 mg)	1.49 (1.04, 2.14)	0.031
Aspirin Use Baseline (81 mg)	1.45 (0.98, 2.13)	0.063
Smoking status (ref: Never)		
Previous smoker	1.35 (0.89, 2.04)	0.161
Current smoker	1.01 (0.61, 1.68)	0.972
Blood group (ref: Group A)		
Blood group B	1.07 (0.56, 2.07)	0.835
Blood group O	0.66 (0.38, 1.14)	0.135
Blood group AB	0.24 (0.03, 1.77)	0.161
Haemoglobin level at follow-up	1.00 (0.92, 1.09)	0.962
Haemoglobin level at baseline	0.83 (0.74, 0.93)	0.001

GIM: Gastric intestinal metaplasia; HR: Hazard ratio; BMI: Body mass index; PPI: Proton pump inhibitors; Neg: Negative; Pos: Positive.

percentage of females affected by GIM compared to males[12], and in a Thai population, the male sex was a risk factor for GIM development[11]. The influence of gender on GIM development might be significant, but our study might have failed to detect it due to the small sample size. Alternatively, gender might have an isolated effect on GIM progression to gastric cancer rather than GIM development.

Non-cardia gastric cancer has a higher incidence rate in certain United States race/ethnicity minorities including, African Americans, Hispanics, and Asians[15]. Previous studies on the United States population have shown that ethnicity is a risk factor for GIM formation, independent of age or *H. pylori* status[16-18]. Non-Hispanic whites have the lowest risk of GIM in comparison to other races/ethnicities. Hispanics, followed by African Americans, carry the highest risk for GIM compared to non-Hispanic whites, which is consistent with other studies[16-18]. Our study also showed African Americans, Hispanics, and other ethnicities/races had an increased risk of GIM compared to Caucasians (Table 2). However, the Hispanic population did not reach the statistical significance level on mult-

Table 3 Multivariate Cox proportional hazards regression model results for gastric intestinal metaplasia formation over time

	HR (95%CI)	*P* value
Age at baseline (ref: ≤ 45)		
46-55	1.75 (0.67, 4.58)	0.255
56-65	1.44 (0.56, 3.68)	0.445
> 65	3.01 (1.25, 7.26)	0.014
Female	0.8 (0.48, 1.33)	0.384
Race/Ethnicity (ref: Caucasians)		
African American	3.4 (1.16, 9.95)	0.026
Hispanic	1.64 (0.28, 9.47)	0.582
Other	7.46 (2.26, 24.67)	0.001
Obesity (BMI > 30)	0.71 (0.42, 1.2)	0.201
Gastritis	1.65 (0.97, 2.81)	0.065
***H. pylori* (ref: Baseline: Neg, follow-up: Neg)**		
Baseline: Neg, follow-up: Pos	1.26 (0.53, 2.98)	0.602
Baseline: Pos, follow-up: Neg	0.6 (0.26, 1.37)	0.223
Baseline: Pos, follow-up: Pos	1.13 (0.34, 3.76)	0.847
Smoking (ref: Never)		
Previous	0.96 (0.56, 1.65)	0.876
Current	0.74 (0.38, 1.47)	0.398

HR: Hazard ratio; BMI: Body mass index; Neg: Negative; Pos: Positive.

ivariant analysis, likely due to the small size of Hispanic population in our study (Table 3). The Asian population is also thought to have a higher risk of GIM, but this population is generally less investigated in United States literature due to the small number of Asians in the United States. Asian and different groups of ethnic and racial minorities were combined as the other ethnic/racial group in our study, this group carried the highest HR when compared to Caucasians. After 5 years of follow-up, close to 25% and 50% of Caucasians and other ethnic/racial groups developed GIM (Figure 1B). Our study is notable that African Americans represent the majority of our study population and carry a higher risk for GIM.

Currently, the AGA recommends surveillance for ethnic/racial minorities only on a conditional basis [2]. Place of birth, rather than ethnicity, was shown to be a risk factor for GIM in one study, where only Hispanics born outside the United States carry a higher risk for GIM compared to Hispanics born in the United States regardless of *H. pylori* status[19]. The effect of place of birth and race on GIM needs further investigation, as it might be a potential factor that affects surveillance.

The impact of *H. pylori* infection on GIM formation and progression was extensively investigated, but the results in the literature were often conflicting thus suggesting the complex role of *H. pylori* in GIM and gastric cancer. *H. pylori* infection is thought to affect the development and progression of GIM[20], but few studies have shown either formation or progression but not both[17]. Ethnicity, genetic makeup, and *H. pylori* virulence factors are additional factors that can further influence the effect of *H. pylori* on GIM[10,18,21]. However, in the present study, no clear effect of *H. pylori* on GIM development was found as shown in other studies[4,19,22]. In our study population, only 13.8% of patients had *H. pylori* infection, which is lower than the reported average *H. pylori* infection in the United States and patients with positive *H. pylori* infection at baseline biopsy, follow-up biopsy, or both seem to have the same risk of developing GIM, not different from those who tested negative for *H. pylori*. However, given the known strong association between *H. pylori* and gastric cancer, we agree with the AGA recommendation for testing and treating *H. pylori* and confirming its eradication, especially if positive in GIM, even though our results did not show a direct effect of *H. pylori* on GIM formation.

Chronic gastritis is part of the Correa cascade, and it precedes GIM development. The long-term effect of *H. pylori*-negative chronic gastritis and its role in the development of GIM have been poorly studied. A prospective study in Thailand investigated 400 patients with chronic gastritis and showed that chronic gastritis is associated with an increased risk for progression regardless of *H. pylori* status[4]. Our study showed that gastritis is associated with GIM formation over time. The gastric inflammation,

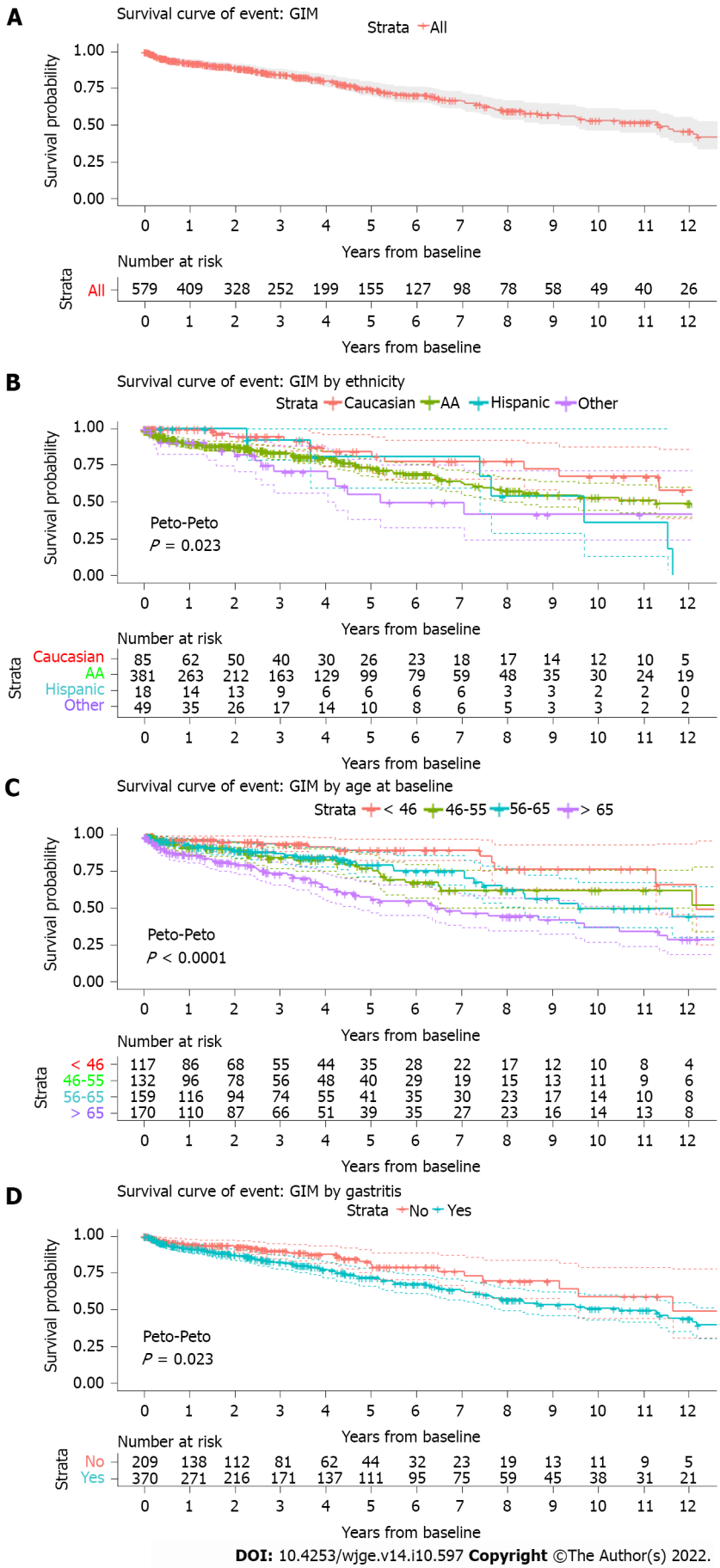

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Figure 1 Survival estimate curve along with population at risk table. A: Estimated probability of not developing gastric intestinal metaplasia at a

respective time interval after baseline without gastric intestinal metaplasia (GIM); B: The estimated probability of not developing gastric intestinal metaplasia in different ethnicities/races at a respective time interval after baseline without GIM; C: The estimated probability of not developing gastric intestinal metaplasia in different age groups at a respective time interval after baseline without GIM; D: The estimated probability of not developing gastric intestinal metaplasia in gastritis compared to no gastritis at a respective time interval after baseline without GIM. GIM: Gastric intestinal metaplasia.

rather than the *H. pylori* infection itself, might be driving GIM formation. On the 12 years survival curve, a significant difference in GIM formation is shown between the group with and without gastritis, noticeable as early as 1 year (Figure 1D). Thus, early recognition and treatment of gastritis can impact GIM formation and possibly prevent GIM thus reducing gastric cancer risk.

The study is limited by its retrospective nature. All the patients in the study are from a single tertiary center in Washington, DC. The standard evaluation of GIM in our pathology lab does not involve further grading or classification, which added to the study's limitation. In spite of the retrospective nature of the study, the strength of our study is its unique study design and distinct study population to assess the longitudinal data over time between upper endoscopies in a single academic center with a predominantly African American population, which has not been adequately investigated in other studies. It is also notable that this study population has a low prevalence of *H. pylori*, thus allowing us to examine other risk factors involved in the development of GIM aside from *H. pylori* infection. Our limitations also include the low number of Asians in our study population who were included as the other ethnic/racial category in our study, thus limiting comparisons with other published studies from Asia.

CONCLUSION

In conclusion, our study demonstrates that race is an important risk factor for GIM and ethnic/racial minorities in the United States carry a higher risk of GIM compared to Caucasians. Older age, especially age group > 65, was associated with higher GIM risk. Gastritis rather than *H. pylori* infection is also associated with GIM formation in our low *H. pylori* prevalent patient population. These risk factors identified in our study will serve as important components in developing risk stratification models for optimal surveillance programs for GIM and gastric cancer.

ARTICLE HIGHLIGHTS

Research background

Gastric intestinal metaplasia (GIM) is a form of gastric pre-malignant lesions. It falls on the spectrum of the Correa cascade. The cascade includes chronic gastritis, atrophic gastritis, GIM, and dysplasia.

Research motivation

We designed this study to investigate factors leading to GIM formation. There is a lack of literature about this topic in the United States, especially among ethnic minorities, which are considered high-risk populations.

Research objectives

We aimed to identify factors that increase GIM formation in high-risk populations. These factors would help guide the future surveillance of selected patients and possibly suggest treatment modalities.

Research methods

This is a retrospective longitudinal study in a tertiary hospital in Washington, DC. The study includes patients with at least two upper endoscopies with gastric biopsies to assess the evolution of GIM over time. A Cox regression model was built to investigate the significant factors over the study time.

Research results

Our study confirms that Ethnicity-Race minorities have a higher rate of GIM formation. We found that gastritis increases GIM formation over time. *Helicobacter pylori* in low-prevalence areas might not be a strong risk factor. Our results emphasize on future surveillance of minorities and management of gastritis as a way to reduce the burden of gastric cancer.

Research conclusions

In conclusion, our study suggests that older age, having gastritis, or being from ethnic-race minorities is associated with an increased risk of GIM.

Research perspectives

Further studies are needed to clarify factors associated with GIM progression and regression. This would help form a complete picture of the development and progression of gastric pre-malignant lesions.

FOOTNOTES

Author contributions: Ahmad AI and Cho W contributed to the study designing and wrote the manuscript; Ahmad AI, Cho W, Lee A and Pothoulakis I contributed to the manuscript edit; Lee A, Caplan C, Wikholm C performed the project coordinator; Lee A, Caplan C, Almothafer Z, Raval N, Marshall S, Hodgins N, Kang IG, Chang RK, Dailey Z, Daneshmand A, Kapadia A, Oh JH, Rodriguez B, Sehgal A, Sweeney M, Swisher CB, Childers DF, Mishra A, O'Connor C and Sequeira LM contributed to the data collection.

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SYSTEMATIC REVIEWS

Water-jet *vs* traditional triangular tip knife in peroral endoscopic myotomy for esophageal dysmotility: A systemic review and meta-analysis

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Abstract

BACKGROUND

Peroral endoscopic myotomy is an increasingly used less invasive modality to treat esophageal dysmotility. Recently, triangular tip knife with integrated water jet function has been introduced to mitigate multiple instrument exchanges.

AIM

To compare traditional triangular tip knife and water jet knife in terms of procedural success, duration, instrument exchanges, coagulation forceps use, and adverse events.

METHODS

We conducted a systemic review and meta-analysis with two authors independently in electronic databases (PubMed, Embase, and Cochrane Library) from inception through May 2021. In addition, we conducted a relevant search by *Reference Citation Analysis* (RCA) (https://www.referencecitationanalysis.com). A fixed-effects model was used to calculate weighted mean, odds ratio (OR), and confidence intervals (CI).

RESULTS

We included 7 studies involving 558 patients. Triangular knife and water jet knife were similar in odds of procedural success with ratio of 4.78 (95%CI = 0.22-102.47) and odds of clinical success with ratio of 0.93 (95%CI = 0.29-2.97), respectively. Water jet knife had fewer instrument exchanges compared to triangular knife (2.21, 95%CI = 1.98-2.45 *vs* 11.9, 95%CI = 11.15-12.70) and usage of coagulation forceps (1.75, 95%CI = 1.52-1.97 *vs* 2.63, 95%CI = 2.37-2.89). Adverse events were higher in triangular knife group (OR: 2.30, 95%CI = 1.35-3.95).

CONCLUSION

Peroral endoscopic myotomy using water jet knife is comparable in terms of pro-

cedural success to triangular tip knife. Water jet knife also required shorter procedural duration, less instrument exchanges, coagulation devices, and overall adverse events.

Key Words: Gastroenterology; Endoscopy gastrointestinal; Esophageal motility disorders; Water jet knife; Dysmotility

Core Tip: Peroral endoscopic myotomy (POEM) has gained traction due to its novel technique of preserving the mucosal layer while working in the submucosa and minimizing risk of leakage of contents into the mediastinum. It hails comparable efficacy and safety data to the standard surgical therapy of laparoscopic Heller myotomy in short term follow up studies. The major steps of POEM are similar among centers, including small mucosal incision, submucosal tunneling, myotomy, and mucosal closure. Within these individual steps, many tools and variations exist to achieve the result. Recently, an innovative water-jet integrated triangular tip knife (WJ) has been devised in order to improve procedural time with less instrument changes, as well as minimize adverse events. There have been several studies comparing the conventional triangular tip knife and WJ and suggesting that WJ can achieve similar clinical and procedural success rate, but with lower adverse effects, instrument changes, and intra-procedural coagulation devices. This is the first meta-analysis to compare the two instruments.

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INTRODUCTION

Idiopathic achalasia is classified as an esophageal motility disorder thought to be related to loss of inhibitory ganglion cells in the esophageal myenteric plexus. This leads to failure of the lower esophageal sphincter (LES) to relax and aperistalsis of the esophageal body[1]. It has an annual incidence of 1 in 100000 and a prevalence of about 10 in 100000[2]. At present-day, there are no curative treatments to reverse loss of neurons, and thus palliative therapies to weaken the LES and allow passive emptying of the esophagus have been implemented. These have ranged from endoscopic pneumatic dilation to invasive measures such as surgical myotomy.

More recently, peroral endoscopic myotomy (POEM) has gained traction due to its novel technique of preserving the mucosal layer while working in the submucosa and minimizing risk of leakage of contents into the mediastinum. It hails comparable efficacy and safety data to the standard surgical therapy of laparoscopic Heller myotomy in short term follow up studies[3,4]. The first endoscopic myotomy was described in 1980 by three Venezuelan gastroenterologists, and later the technique refined with a submucosal tunnel based on two USA publications in 2007 performed on pigs[5-7]. POEM as we know it today, was initially performed on 17 achalasia patients by Inoue *et al*[8] in a groundbreaking study in 2010.

The major steps of POEM are similar among centers, including small mucosal incision, submucosal tunneling, myotomy, and mucosal closure. Within these individual steps, many tools and variations exist to achieve the result. Traditionally, the knife that has been used is a conventional triangular tip knife (TT), which is an electrosurgical knife that has a conductive triangle tip for cutting mucosa. Cutting mucosa can be performed in any direction without rotating the knife, making it suitable for marking, incision, and dissection. Recently, an innovative water-jet integrated triangular tip knife (WJ) has been devised in order to improve procedural time with less instrument changes, as well as minimize adverse events. It comprises a thinner and more compact tip as well as jet function to allow saline injection after cutting without the need to switch devices (Figures 1 and 2). There have been several studies comparing the conventional triangular TT and WJ and suggesting that WJ can achieve similar clinical and procedural success rate, but with lower adverse effects, instrument changes, and intra-procedural coagulation devices[9].

Current literature lacks high-quality evidence to compare clinical outcomes of WJ and TT knives in POEM used for esophageal dysmotility disorders. The purpose of our systemic review and meta-analysis is to compare WJ and TT in terms of procedural and clinical success, and determine whether fewer adverse events and instrument changes could be achieved with the decreased procedural duration.

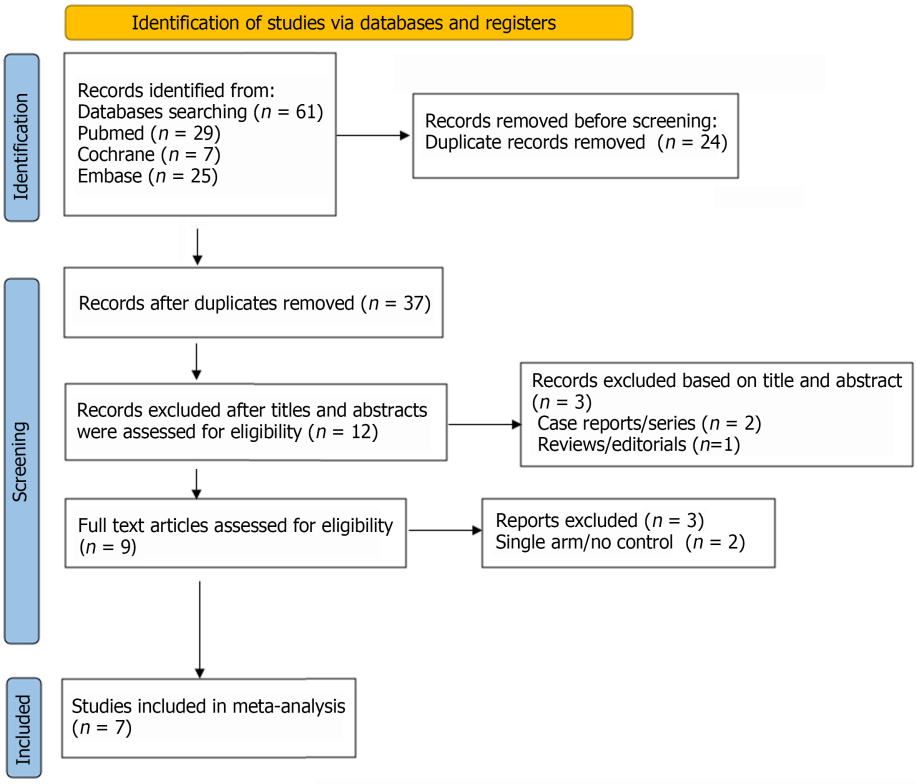

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Figure 1 Flow diagram with search results and selection criteria.

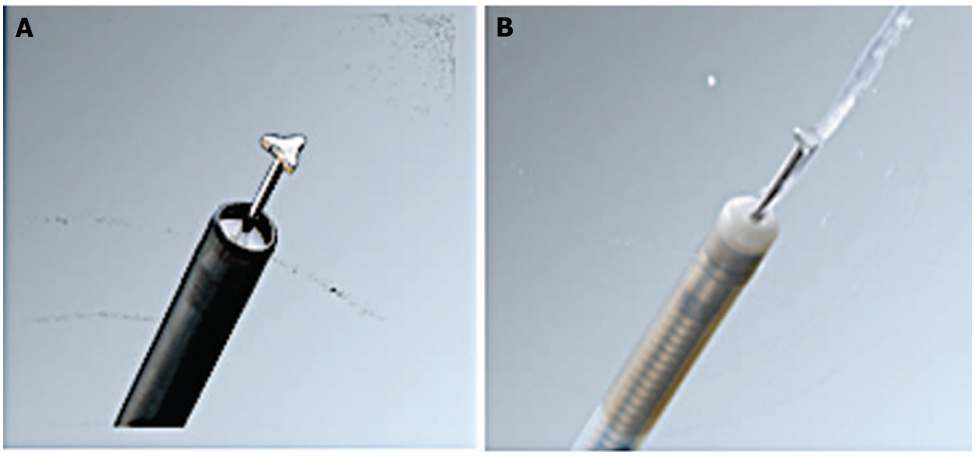

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Figure 2 It comprises a thinner and more compact tip as well as jet function to allow saline injection after cutting without the need to switch devices. A: Conventional triangular tip knife; B: Water-jet integrated triangular tip knife.

MATERIALS AND METHODS

Study selection criteria

Studies using triangular tip knife with integrated water jet as the instrument for peroral endoscopic myotomy were selected. Inclusion criteria included both adults and children with an indication of esophageal motility disorders for POEM treatment. Each study used POEM for achalasia, while 1 study did include other indications of diffuse esophageal spasm, nutcracker esophagus, and non-relaxing lower esophageal sphincter. Studies included patients that had been treated with prior therapies before POEM, of which majority were pneumatic balloon dilation.

Data collection, extraction, and quality assessment

Studies were systemically searched independently by two investigators (Belopolsky Y and Puli SR) in

Pubmed, Cochrane, and EMBASE. The search was performed from inception to May 2021. The search terms used were "peroral endoscopic myotomy" and "knife". Each abstract and title were screened for eligibility. All references at the end of each selected article were explored manually to retrieve additional studies. Any differences among investigators were resolved by mutual agreement. The interobserver variability was 1. The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation methodology[10]. The agreement between reviewers for the collected data gave a Cohen κ value of 1.0.

Statistical analysis

This meta-analysis was performed by calculating weighted pooled effect *i.e.,* weighted pooled effect of patients with procedural success. First the individual study weighted pooled effect of procedural success was transformed into a quantity using Freeman-Tukey variant of the arcsine square root transformed proportion. The pooled proportion is calculated as the back-transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the Mantel-Haenszel Method (fixed effects model) and DerSimonian-Laird Method (random effects model)[11,12]. Random effect model was used for meta-analysis in case of heterogeneity being statistically significant otherwise fixed effect models were applied. Forest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the Forest plots indicates the assigned weight to that study. In addition, odds ratio was used to represent dichotomous outcomes with a 95% confidence interval (CI), where a p value of <0.05 was considered statistically significant. The heterogeneity among studies was tested using I^2 and Cochran's Q test based upon inverse variance weights[13]. I^2 of 0% to 39% was considered as non-significant heterogeneity, 40% to 75% as moderate heterogeneity, and 76% to 100% as considerable heterogeneity. If P value is > 0.10, it rejects the null hypothesis that the studies are heterogeneous. The effect of publication and selection bias on the summary estimates was tested by both Harbord-Egger bias indicator and Begg-Mazumdar bias indicator[14]. Also, funnel plots were constructed to evaluate potential publication bias using the standard error and diagnostic odds ratio[15,16].

RESULTS

Characteristics of studies

A total of 61 studies were retrieved by our search strategy. We reviewed these and excluded 52 studies based on titles and abstracts and reviewed full texts of remaining 9 studies. Finally, 7 studies met our inclusion and exclusion criteria[9,17-21]. This consisted of 2 randomised controlled trial (RCT) and 5 retrospective single center cohorts published between 2012 and 2021. Five studies were published full text articles while two studies were available as abstract poster presentations. Figure 1 shows the PRISMA flow chart to illustrate how final studies were selected. All pooled estimates were calculated using fixed and random effects models. The pooled effects estimated by both models were similar. All the pooled estimates given below are from the fixed effect model. Heterogeneity was assessed with *I*-squared, and publication bias with Egger's test.

A total of 558 patients were included in this meta-analysis. The mean age of patients' was 42.82 years (SD = 7.86) in the TT group and 37.03 years (SD = 12.29) in the WJ group, of which 59.57% were male in TT *vs* 52.51% in WJ group.

This review analyzed the various outcomes including procedural success, clinical successes defined as < 3 Eckardt score post-POEM, procedure duration, number of instrument exchanges, and usage of coagulation forceps. Most, but not all studies, included information on every variable that was analyzed. The studies that included information on the specific variable were included in the final analysis of that variable.

Clinical and technical success

Analysis showed weighted odds of technical success for POEM in TT group compared to WJ group to be 4.78 (95%CI = 0.22-102.47). In terms of clinical success, the standard accepted definition is a score of three or below in Eckardt score. The TT group had weighted odds of clinical success compared to WJ of 0.93 (95%CI = 0.29-2.97) (Figure 3). Publication bias calculated using Begg-Mazumdar gave Kendall's tau b value of -0.33 (P = 0.33). Heterogeneity calculated using I^2 was 0 indicating no significant heterogeneity among studies.

Procedural duration, number of instrument changes, and usage of coagulation forceps

Analysis of procedural duration for WJ had a weighted mean duration of 31.63 min (95%CI = 29.44-33.82) as compared to TT with weighted mean duration of 50.45 min (95%CI = 47.35-53.55). Regarding instrument changes, analysis showed a weighted number of instrument changes for TT of 11.92 times (95%CI = 11.15-12.70) *vs* WJ with weighted number of instrument changes of 2.21 times (95%CI = 1.98-2.45). The usage of coagulation forceps analysis showed for WJ the weighted usage of coagulation

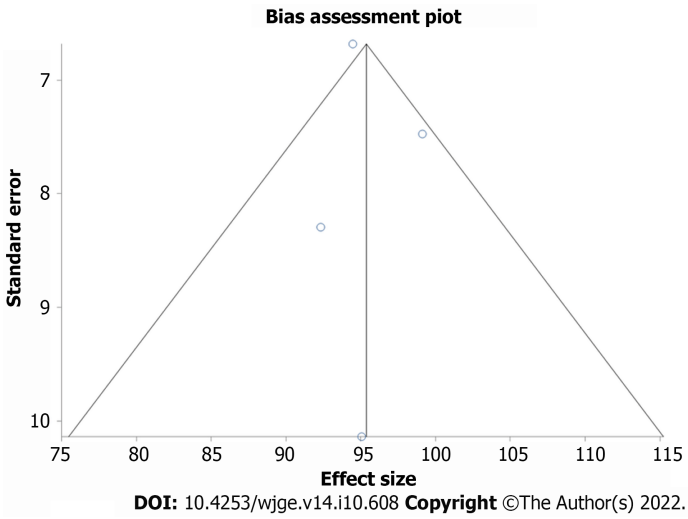

Figure 3 Funnel plot for publication bias of clinical success of triangular tip knife and water-jet integrated triangular tip knife.

forceps to be 2.63 times, (95%CI = 2.37-2.89) *vs* TT with weighted usage of coagulation forceps to be of 1.75 times (95%CI = 1.52-1.97).

Adverse events

The overall adverse events of TT compared to WJ had a pooled OR of 2.34 (95%CI = 1.34-4.23) (Figure 4). When evaluating the adverse event of subcutaneous emphysema, TT had a pooled OR of 1.46 (95%CI = 0.83-2.59) compared to WJ.

DISCUSSION

We performed a systemic review and meta-analysis of studies that compared conventionally used triangular tip knife and a knife using new integrated water-jet technology, in terms of several peri- and post-procedural outcomes. There was comparable procedural as well as clinical success, defined as post-operative Eckardt score of 3 or lower.

By pooling data across studies, our meta-analysis showed that WJ had statistically decreased procedural time of 32 min as compared to the TT of 50 min. For the endoscopist, that could theoretically increase procedural productivity. In addition, our analysis showed that both instrument exchanges and usage of coagulation forceps were decreased in the WJ group when compared to the TT group. Likely this can partially explain the shorter procedural duration, as well as indicate less intra-procedural bleeding with the less use of coagulation instruments.

The frequently reported adverse events of POEM include pneumomediastinum, mucosal perforations, pneumothorax, mucosal perforations, and subcutaneous emphysema[22]. In our meta-analysis, statistically adverse events were less likely to happen in the WJ group compared to the TT group. However, when examining one adverse event commented on in each study of subcutaneous emphysema, this was comparable among both groups as the confidence interval crossed one. Thus while overall adverse events were lower, it is difficult to discern which, if any, WJ could have lower risk of provoking.

Our study is the first in the literature to assess TT and WJ knives in POEM procedures for esophageal dysmotility disorders and analyze their effectiveness for the procedure. There are several strengths to our review. First, we included studies of WJ compared to standard TT technique, including 2 RCT. This allowed a more valuable comparison of procedural outcomes. Second, we conducted a systemic literature review with well-defined inclusion criteria, as well as careful exclusion of redundant studies with detailed extraction of data. Third, we separated studies that did not evaluate esophageal dysmotility disorders specifically, due to variable intra-procedural techniques that could have skewed the data.

While this study has included the most recent randomized controlled trials, these are few in our current available literature. Second, our conclusions apply to achalasia primarily, and did not include other indications for POEM other than those related to esophageal motility disorders. Finally, blinding of endoscopists was not possible and thus performance bias could have played a factor as well as inability to assess each performing endoscopist's skill level.

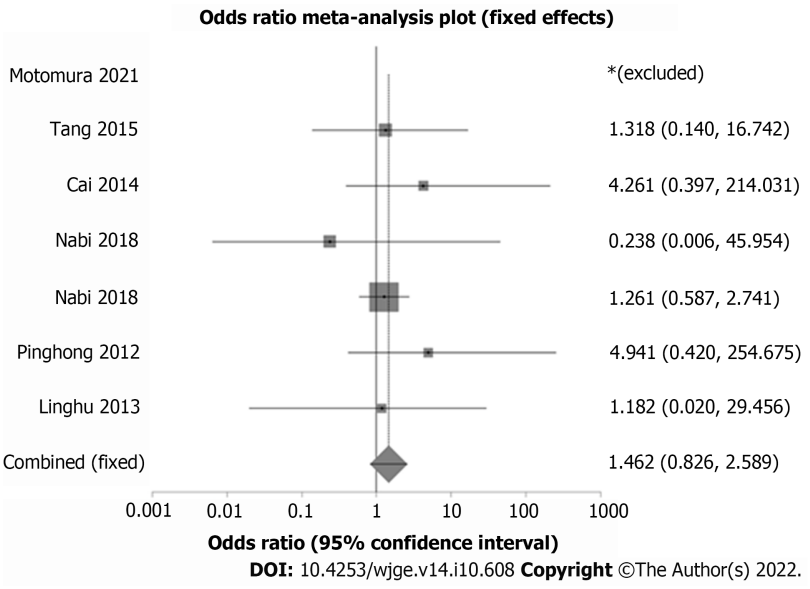

Figure 4 Forest Plot for assessing the odds ratio of adverse effects between usage of water-jet integrated triangular tip knife and triangular tip knife.

CONCLUSION

Water jet triangular tip knife has decreased procedural duration, number of instruments used, and usage of coagulation forceps over the conventional triangular tip knife. As such, this modality represents an attractive option for POEM. Our review represents the first review of the literature regarding water jet triangular tip knife in the management of esophageal dysmotility disorders using POEM. Collectively, the data supports using water jet triangular tip knife as a primary modality in terms of safety for the patient with less adverse events, with comparable technical and clinical success to the conventional triangular tip knife.

ARTICLE HIGHLIGHTS

Research background

This study is the first metanalysis to discover the differences between two main modalities for performing peroral endoscopic myotomy.

Research motivation

This study allows us to continue progressing in terms of instruments as it leads to continued success, but quicker and less adverse outcomes.

Research objectives

To compare two knives, conventional triangular tip as well as water jet integrated triangular tip knives.

Research methods

Clinical trials were examined and put together into metaanalysis.

Research results

This shows that water jet knife is comparable in terms of success to conventional traditional triangular knife with fewer adverse events and faster time.

Research conclusions

This study proposes new availability in instruments to the field of endoscopic myotomy.

Research perspectives

This allows future research to examine additional instruments and how to continue to further clinical success with better outcomes as well as ease for the endoscopist.

FOOTNOTES

Author contributions: Belopolsky Y and Puli SR contributed equally and substantially to the conception and design of the work, analysis, acquisition, interpretation of data for the work, and drafting the work and revising for important intellectual content; Belopolsky Y and Puli SR agree to be accountable for all aspects of work in ensuring questions related to accuracy and integrity of any part of the work are appropriately investigated and resolved; all authors wrote, read and approved the final manuscript.

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SYSTEMATIC REVIEWS

Laparoscopic Janeway gastrostomy as preferred enteral access in specific patient populations: A systematic review and case series

Max Murray-Ramcharan, Maria Camilla Fonseca Mora, Federico Gattorno, Javier Andrade

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Grade D (Fair): 0
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Abstract

BACKGROUND

Nutrition is one of the fundamental needs of both patient and non-patient populations. General trends promote enteral feeding as a superior route, with the most common enteral access being the percutaneous endoscopic gastrostomy (PEG) as the first-line procedure, with surgical access including Witzel gastrostomy, Stamm Gastrostomy, Janeway gastrostomy (JG) as secondary means.

AIM

To describe cases and technique of laparoscopic Janeway gastrostomy (LJG) and perform a systematic review of the data.

METHODS

We successfully performed two LJG procedures, after which we conducted a literature review of all documented cases of LJG from 1991 to 2022. We surveyed these cases to show the efficacy of LJG and provide comparisons to other existing procedures with primary outcomes of operative time, complications, duration of gastrostomy use, and application settings. The data were then extracted and assessed on the basis of the *Reference Citation Analysis* (https://www.referencecitationanalysis.com/).

RESULTS

We presented two cases of LJG, detailing the simplicity and benefits of this technique. We subsequently identified 26 articles and 56 cases of LJG and extrapolated the data relating to our outcome measures. We could show the potential of LJG as a viable and preferred option in certain patient populations requiring

enteral access, drawing reference to its favorable outcome profile and low complication rate.

CONCLUSION

The LJG is a simple, reproducible procedure with a favorable complication profile. By its technical ease and benefits relating to the gastric tube formed, we propose this procedure as a viable, favorable enteral access in patients with the need for permanent or palliative gastrostomy, those with neurologic disease, agitation or at high risk of gastrostomy dislodgement, or where PEG may be infeasible.

Key Words: Laparoscopic Janeway gastrostomy; Janeway; Nutrition; Feeding tube; Enteral access; Reproducible

Core Tip: This systematic review identifies that the laparoscopic Janeway gastrostomy may be advantageous as a first line option for enteral access in specific patient populations, when compared to percutaneous endoscopic gastrostomy, or other surgical gastrostomy options, by virtue of the gastric tube created and its resistance to dislodgment and ensuing complications. Patients with high risk for tube dislodgment, including those with neurocognitive disorders, seizures, dementia, or patients requiring permanent enteral feeding access, may benefit the most from this intervention as a first-line option.

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INTRODUCTION

Nutrition is one of the fundamental needs of the hospitalized patient, with feeding access providing many unique challenges within different patient subgroups. From stable patients to those requiring intensive care unit treatment, all have specific metabolic demands and requirements necessary for progression towards optimization. Within a hospital setting, there have been extensive studies examining differences in outcomes between enteral feeds and parenteral routes, and many recent meta-analyses advocate for the use of enteric feeds either alone or supplemented by parenteral nutrition. Benefits identified include decreased incidence of respiratory infections, length of stay in the hospital [1], decreased morbidity and mortality, preservation of bowel function[2], and others. Nasogastric or nasoenteric tubes are typically the first-line forms of access in patients who require enteral feeds and are poorly suited for long term use due to discomfort from the tube, the unwillingness of conscious patients to endure placement, and other mechanical adverse features including frequent dislodgement or removal of tube and epistaxis from trauma during placement[3], and similar rates of aspiration events with both nasogastric and nasojejunal tubes[4]. Abnormal esophageal, pharyngeal or gastric anatomy may contribute to failure or difficulty of placement. Nasogastric or nasoenteric feeds are used for more short-term scenarios (less than 4 wk), whereas those requiring feeding for typically more than 6 wk may benefit from a gastrostomy[5].

For long-term feeding accesses, the percutaneous endoscopic gastrostomy (PEG) or percutaneous radiographic endoscopy (PRG)[6,7] remain the first line and preferred procedure. First described in the literature in 1980, the PEG has become widely popularized due to simplicity of performance, ability to perform as a bedside procedure, cost-effectiveness, and low complications profile by non-surgical approach[8]. What historically was the only viable option for feeding access, now the second line in the event of failure or infeasibility of PEG, exists the surgical gastrostomies (and jejunostomies). The Stamm gastrostomy, introduced in 1894[9]; is achieved *via* an incision made in the anterior stomach wall with a purse-string suture securing a tube brought out through the anterior abdominal wall. Performed open or laparoscopically, this technique is simple to perform with low morbidity and revision rates[10]. The Witzel gastrostomy, initially described in 1891, is performed with a tube or catheter (exiting the anterior abdominal wall) introduced into a gastrostomy on the anterior stomach, with parallel folds fashioned into a tunnel around the tube. This procedure had limited response as a gastrostomy, and multiple variations have led it to be performed instead as a jejunostomy creation technique. As a result, this is a rarely performed gastrostomy procedure with minimal literature documenting its utility as such[9]. The Janeway gastrostomy, the focus of this paper, was introduced into practice in 1913, with the unique

creation of a gastric tube from the anterior stomach wall exteriorized as a stoma boasts the advantage of permanence and resilience in the setting of tube dislodgement in comparison with other techniques[9]. Initially used for feeding in cases of advanced head and neck tumors[11], following several modifications, this technique is commonly performed laparoscopically for a variety of indications. This literature review explores the versatility of the laparoscopic Janeway gastrostomy (LJG) for patients requiring long-term or permanent enteral feeding access with the aid of two presented cases.

MATERIALS AND METHODS

We retrieved the records of the patients who underwent LJG creation on (n = 2) in Woodhull Hospital Center of New York Health and Hospitals (Brooklyn, New York) from 2021 to 2022. Two patients were identified and their respective clinical courses relevant to their procedure were documented, making note of technical details, ensuing postoperative courses and complications.

Search strategy for systematic review

A comprehensive search of the literature was conducted through MEDLINE/PubMed, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews to identify relevant articles. Before initiation of the search authors determined titles, keywords, and text words of importance to apply in the search. The database search included a combination of the following keywords: Janeway and gastrostomy. Cross-referencing was then performed to identify additional relevant articles. A data collection form was used to extract pertinent information including inte-rvention, treatment, and various outcome measures.

Study selection and characterization of articles

Relevant studies were identified and selected by individual reviewers separately based on title and abstract content. Supporting evidence included randomized and non-randomized controlled trials, systematic reviews, prospective and retrospective studies, case series, reviews, and letters to editors. Analysis and evaluation of Spanish articles were performed independently by native Spanish-speaking physicians.

Inclusion and exclusion criteria

The articles included in this selection were English or Spanish articles published between 1984 and 2022. We included patients of all ages and articles of all types. Exclusion criteria consisted only of articles written in other languages such as French or German, to prevent inaccurate translation. This search was performed and reviewed for inclusion in the review by authors MMR and MCF independently on 22nd February 2022.

Quality assessment

The methodological quality of the studies was assessed using the 2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practices Guidelines: Evidence Rating (Table 1). Data quality and recommendations for clinical application were categorized based on the evidence level.

RESULTS

Systematic review

An initial assessment of articles' abstracts and titles was performed with a total preliminary outcome of 26 articles. After this initial screening, the 26 articles were evaluated in more detail with proper screening against inclusion and exclusion criteria. 15 articles were excluded; of those three had content in German and two in the French language, the remaining twelve referred to content that was not pertinent to the outcomes being evaluated in this review, by either discussing animal trials or JG for additional procedures (trans-gastric endoscopic retrograde cholangiopancreatography in complicated anatomy) rather than enteral access. An addition of five references was found and of those, three were included after cross-referencing articles. After a thorough selection of articles using the PRISMA criteria (Figure 1) a total of 11 articles resulted in the following breakdown: Five case series, one case report, two short communications articles with associated case reports, one technical innovation article with associated case series, one comprehensive review article, and one original article.

Results from a systematic review

From the analyzed studies on LJG (Table 2), of the total 56 patients with LJG 43 patients had documented their operative times, of which the total average was 37.66 min (40 min by Ritz *et al*[12], 35 min

Table 1 2010 American association of clinical endocrinologists protocol for production of clinical practices guidelines - evidence rating

Numerical descriptor (evidence level)	Semantic descriptor (reference methodology)
1	Meta-analysis of randomized controlled trials
1	Randomized controlled trial
2	Meta-analysis of nonrandomized prospective or case-controlled trials
2	Nonrandomized controlled trial
2	Prospective cohort study
2	Retrospective case-control study/Retrospective cohort study
3	Cross-sectional study
3	Surveillance study (registries, surveys, epidemiologic study)
3	Consecutive case series
3	Single case reports
4	No evidence (theory, opinion, consensus, or review)

1 = strong evidence; 2 = intermediate evidence; 3 = weak evidence; 4 = no evidence. CCS: Consecutive case series; CSS: Cross-sectional study; MRCT: Meta-analysis of randomized controlled trials; MNRCT: Meta-analysis of nonrandomized prospective or case-controlled trials; NRCT: Nonrandomized controlled trial; NE: No evidence; PCS: Prospective cohort study; RCCS: Retrospective case-control study; RCS: Retrospective cohort study; RCT: Randomized controlled trial; SS: Surveillance study; SCR: Single case reports.

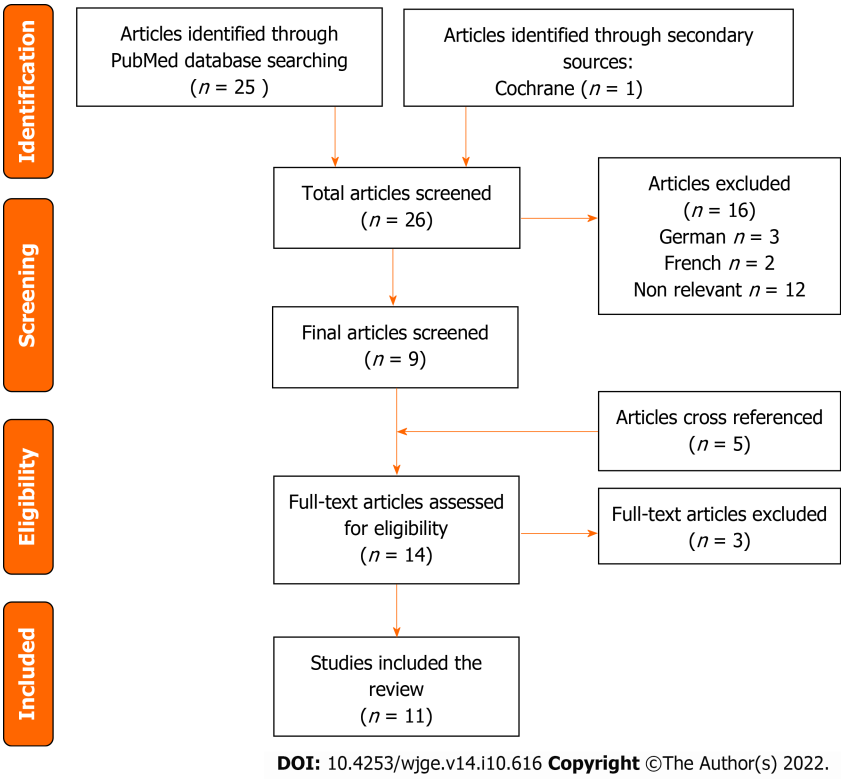

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Figure 1 PRISMA flow chart for articles and studies selection.

by Serrano *et al*[13], and 38 min by Raakow *et al*[14]). Mean usage times (MUTs) were documented in 36 patients and 3 articles. We noted 13 total complications and 0 mortalities related to the procedure. For the 102 patients that underwent open Janeway gastrostomies (OJG) (Table 3); twelve patients had documented MUTs, however none of them had anticipated future removal at the time of documented follow-up. Of this the average follow-up was 7.5 mo (9 mo reported by Koivusalo *et al*[15], and six months by Abdel-Lah *et al*[16] The remaining authors did not consider this as an endpoint.

Table 2 Literature reported cases of laparoscopic Janeway gastrostomies

Ref.	Evidence rating	Case	Outcomes	Complications
Haggie *et al*[18], 1992	3	*n* = 1 pt; Age= 65 yr (M); Esophageal occlusion of pharyngeal SCC s/p CTX and RTX	ORT: N/M; MUTs: 3 wk (death 2/2 primary disease)	Leakage of gastric contents easily managed; D: 1; R: 1; TC: 2
Serrano *et al*[13], 1994	3	*n* = 7 pt; Age = 48-83 yr; Esophageal cancer stage IV: 85% (*n* = 6); Traumatic peri-esophageal hematoma: 14.2% (*n* = 1)	ORT: 30-40 min. Average 35 min. MUTs: N/M	TC: 0; D: 0; R: 0; Mortality: 0
Ritz *et al* [12], 1998	3	*n* = 15 pt; Age average: 61 yr; Esophageal or paraesophageal tumors	ORT: 20-55 min. MUTs: 3.5 mo (death)	Stoma necrosis to Witzel gastrostoma: 6.6% (*n* = 1); Self-limiting skin irritation: 20% (*n* = 3); D: 0; R: 0; TC: 2
Molloy M *et al*[17], 1997	3	*n* = 2 pt (M); Age= 63 yr and 77 yr; Organic neurologic disorders + pulled out PEG (placed 48 h prior); Perforation along greater curvature (minimal contamination)	ORT: N/M. MUTs: N/M	C: N/M; D: N/M; R: N/M
Raakow *et al*[14], 2001	2	*n* = 21 pt (19 M; 2 F); Age = 53-78 yr; Extensive tumors of: Hypopharynx 57.1% (*n* = 12) Esophagus 42.8% (*n* = 9); Prior UGI surgery 19% (*n* = 4) to (2 OCh, 1 PCJ, 1 repair DP)	ORT: 24-50 min. Average 38 mins. MUT: 3.4 mo 2/2 death due to primary	C: Self-limiting skin irritation (method dependent): 9.6% (*n* = 2); D: N/M; R: N/M; Mortality from advanced cancer; MUTs: 26 d to 6.5 mo (average 3.4 mo)
Tous Romero *et al*[19], 2012	2	*n* = 57 pt; Age = 51 yr; 10 LJG, 47 OJG; Esophageal cancer: 38.6% (*n* = 22); Head & neck: 26.3% (*n* = 15); Neuro deficit 26.3% (*n* = 15)	ORT: N/M. MUTs: N/M	TC: 5 (some patients had multiple complications); D: N/M; R: N/M; Gastric content leakage: 30% (*n* = 3); Abd wall irritation: 30% (*n* = 3); No C: 50% (*n* = 5); Exudate: 10% (*n* = 1); Exudate with + culture: 20% (*n* = 2); Granuloma: 10%(*n* = 1); Balloon rupture: 10% (*n* = 1); Loss of peristomal content: 0

C: Complications; CXT: Chemotherapy; D: Dislodgement; DPr: Duodenal perforation; F: Female; M: Male; GT: Gastric tube; LJG: Laparoscopic Janeway gastrostomy; JT: Jejunostomy tubes; LE: Life expectancy; MUTs: Mean usage times; n: Number of patients; N/M: Not mentioned; OCh: Open cholecystectomy; ORT: Operating time; Pt: Patients; PCJ: Pancreatic cyst jejunostomy; R: Replacement; RXT: Radiotherapy; SG: Stamm gastrostomy; SCC: Squamous cell carcinoma; UGI: Upper gastrointestinal.

Laparoscopic Janeway gastrostomy technique

There exist several modifications of the original JG, with further modifications introduced with the inception of laparoscopy into commonplace surgical practice[14]. We describe the laparoscopic technique used in the ensuing case presentations. The patient was placed supine with a slight reverse Trendelenburg to better visualize the stomach. Port sites were placed as follows, a 12 mm supraumbilical port, a 5 mm port to the right of the umbilicus and a 12 mm in the left upper quadrant. The anterior surface of the stomach along the greater curvature was retracted towards the anterior abdominal wall (Figure 2A), and an EndoGIA stapler 45 mm purple cartridge was used *via* the right 12 mm port to create a gastric tube approximately 5 cm - 6 cm in length, 1cm wide, by described Janeway technique (Figure 2B). The gastric tube was brought out of the abdomen *via* the leftmost port. A Carter-Thomason trans-fascial port closure device was used to place 3 sutures circumferentially around the base of the gastric tube, anchoring it to the anterior abdominal wall (Figure 2C). Pneumoperitoneum was discontinued to evaluate the resting anatomic position of gastrostomy. The now externalized tip of the gastric tube was then opened and matured to the skin in standard fashion. The matured gastrostomy was then cannulated with a 24 Fr Gastrostomy tube. Pneumoperitoneum was re-established under low pressure and gastrostomy and staple line inspected, demonstrated gastrostomy tube in a good position with the intragastric balloon inflated, and no evidence of immediate complications. The operation was completed with discontinuation of pneumoperitoneum and removal of trocars with appropriate port site closure.

Cases series

Patient A: This is a 77-year-old woman with a past medical history of dementia, hypertension, and depression who was being managed in the hospital for altered mental status and mental decline following infection with coronavirus disease 2019 (COVID-19) a few months prior (Table 4). During the hospital stay, the patient experienced a further decline from baseline, with worsening dementia and refusal of oral intake and malnutrition. The primary team requested enteral feeding access, and with the agreement of the patient's healthcare proxy, we advocated for LJG tube placement. We suggested this procedure due to the patient's dementia, need for permanent/long-term feeding, and a high risk of the patient pulling out tubes. The procedure was performed by the technique described above, and the patient was followed postoperatively. There were no noted complications, and the gastrostomy tube

Table 3 Literature reported cases of open gastrostomies

Ref.	Evidence rating	Case	Outcomes	Complications
McGovern *et al* [21], 1984	3	*n* = 14 children (> 7lb); Severe cerebral palsy without pharyngeal musculature coordination and risk of aspiration	ORT: N/M, MUTs: N/M	C: GT stenosis treated with dilation: 7.14% (*n* = 1); Stomal granulations treated with cautery: 7.14% (*n* = 1); Mortality: 0; D: N/M; R: N/M
Laughlin *et al* [20], 1989	3	*n* = 5 pt. Advanced esophageal cancer; Age/gender: N/M	ORT/MUTs: N/M	C: Stomal tip necrosis with stomal stenosis: 20% (*n* = 1); Mortality: 0; D: N/M; R: N/M
Vassilopoulos *et al*[11], 1998	3	*n* = 24 pt (21M; 3F); Age average: 67.19 yr; Advanced head/neck cancer; Advanced UGI malignancy: 1.2% (*n* = 5); Prior UGI surgery: 0.48% (*n* = 2)	ORT: < 40 min; MUTs: N/M	C: Midline wound SSI treated with antibiotics: 16.6% (*n* = 4); Mortality: 0; D: N/M; R: N/M
Koivusalo *et al* [15], 2006	33	*n* = 4 pt; Age = 0-6 yr; Recurrent gastrostomy prolapses and peristomal infection undergoing modified OJG revision; 3: OSG to 2 closure + PEG; 1: Initial PEG; Prior abdominal surgeries (OGT/PEG)	MUTs: 9 mo	C: 0;D: N/M; R: N/M content
Abdel-Lah *et al* [16], 2006	3	Total procedure 287: JT: 46% (*n* = 167); SG: 18% (*n* = 40); OJG: 4% (*n* = 8); SNY double lumen: 32% (*n* = 72); Head & neck cancer; Total permanent gastrostomies *n* = 27: Balloon catheter/Fontan (LE < 37 d): *n* = 19; OJG (LE > 6 mo): *n* = 8	MUTs; JG = 164 d	Morbidity 12.5% (*n* = 5): D (Migration)/peristomal abrasion- no fixation to parietal peritoneum; Mortality (open jejunostomy) 4.2% (*n* = 12); Esophageal 3% (*n* = 9); Esophagojejunal: 1.2% (*n* = 3); R: N/M
Tous Romero *et al* [19], 2012	2	*n* = 57 pt; Age average: 57, 51 yr 10 LJG, 47 OJG; Esophageal cancer: 38.6% (*n* = 22); Head & neck: 26.3% *n* = 15); Neuro deficit: 26.3% (*n* = 15)	ORT/MUTs: N/M	Gastric content leakage: 89.4% (*n* = 42); Abd wall irritation: 83% (*n* = 39); No C: 2.1% (*n* = 1); Exudate: 23.4% (*n* = 11); Granuloma: 4.3% (*n* = 4); Balloon rupture: 21.3% (*n* = 10); Loss of peristomal content: 17% (*n* = 8)

C: Complications; CXT: Chemotherapy; D: Dislodgement; DPr: Duodenal perforation; F: Female; M=Male; GT: Gastric tube; GC: Great curvature; LJG: Laparoscopic Janeway gastrostomy; JT: Jejunostomy tubes; LE: Life expectancy; MUTs: Mean usage times; *n*: Number of patients; N/M: Not mentioned; OCh: Open cholecystectomy; OJG: Open Janeway gastrostomy; ORT: Operating time; Pt: Patients; OSG: Open stamm gastrostomy; PCJ: Pancreatic cyst jejunostomy; R: Replacement; RXT: Radiotherapy; SG: Stamm gastrostomy; SCC: Squamous cell carcinoma; SSI: Surgical site infection; UGI: Upper gastrointestinal.

Table 4 Our case series of post coronavirus disease 2019 era

Case	Selection of LJG *vs* others	Indications	Outcomes	Complications
Patient A: 77 yr female	Instead of PEG; Patient is high risk of pulling out tubes	Worsening dementia and AMS. Need for long term/permanent feeding	ORT: 87 min. MUTs: 3 mo	D: 0; R: 0; TC: 0
Patient B: 58 yr male; s/p tracheostomy and recent PEG tube placement	Instead of PEG. C: Dislodgement of PEG and septic shock	Cerebral palsy, seizure disorder self-removed PEG. Prior PEG removal + replacement	ORT: 76 min. MUTs: 3 mo	D: 0; R: 0; TC: 0

LJG: Laparoscopic Janeway gastrostomy; PEG: Percutaneous endoscopic gastrostomy; D: Dislodgement; R: Replacement; C: Complications; N/M: Not mentioned; MUTs: Mean usage times; ORT: Operating time.

was used for feeding immediately postoperatively without any complications noted and was discharged safely the following day. The gastrostomy tube remained intact with no complications until the patient passed away as a result of complications of primary disease while in hospice care 3 mo later.

Patient B: This is a 58-year-old man who resides in a nursing home, with a past medical history of cerebral palsy, seizure disorder, diabetes, hypertension, and a past surgical history of tracheostomy and recent PEG tube placement after distant COVID-19 pneumonia (Table 4). After the PEG was placed, the patient was discharged back to his nursing home once his pneumonia resolved, during which time he removed his PEG tube in instances of agitation multiple times, each with subsequent replacement. Several months after initial placement, the patient was brought to the emergency department in septic shock with a tender and distended abdomen. Due to his neurologic conditions, he was unable to provide any history, and he underwent a computed tomography scan which revealed that the balloon of his gastrostomy feeding tube was embedded in the anterior abdominal wall, and there was significant subcutaneous air and fluid along the rectus sheath adjacent to the gastrostomy tube along with a fragment of the apparatus within the stomach. (Figure 3A and B). He underwent an emergent surgery where tube feeds and purulent fluid were found within the soft tissue above the fascia and the

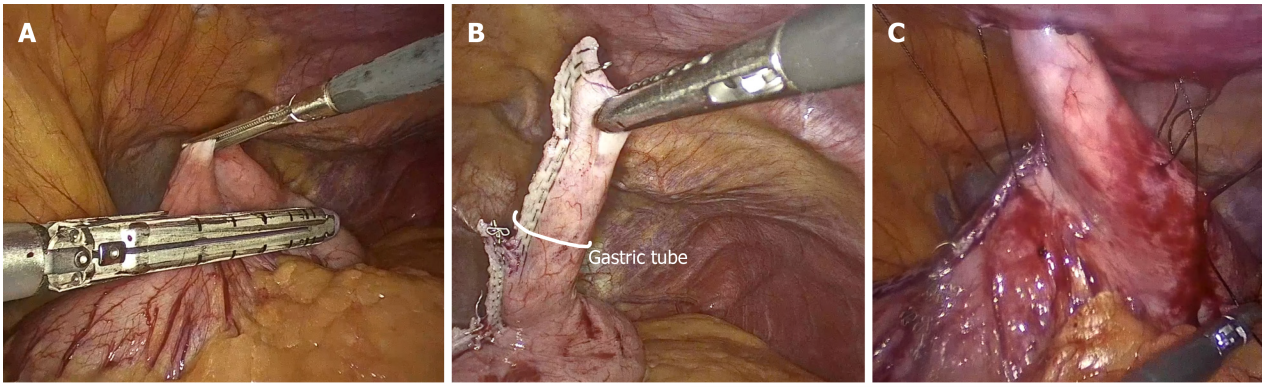

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Figure 2 The anterior abdominal wall of laparoscopic Janeway gastrostomy technique. A: Positioning of stapler for gastric tube creation along greater curvature; B: Gastric tube demonstration; C: Gastric tube being externalized and placement of anchoring sutures.

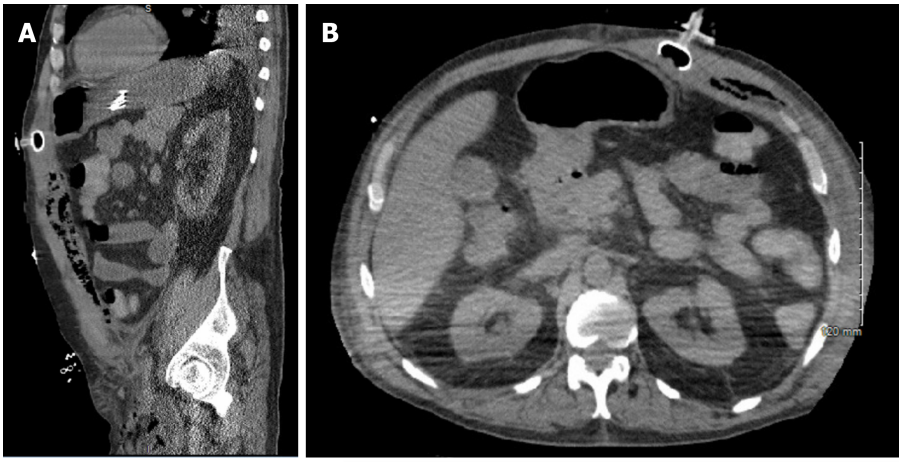

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Figure 3 Computer tomography images related to case B. A: The sagittal view; B: The Axial view.

abdominal cavity. He underwent debridement and washout of this fluid, fascia closed and the wound was left to heal by secondary intention. After he recovered from septic shock in the intensive care unit, a skin graft was performed due to poor healing from this procedure (Figure 4A and B). Due to his hostile anatomy after these procedures, his high risk of removal or dislodgement of the tube, and the continued need for permanent feeding access due to his cerebral palsy, we elected to perform LJG. The procedure was by the technique described above, and the patient was followed postoperatively. There were no noted complications, and the gastrostomy tube was used for feeding immediately postoperatively. The gastrostomy tube was removed by the patient twice within the first 3 wk postoperatively (postoperative days 11 and 18), and two more times within the first 2 mo post-procedure (postoperative days 48 and 61) with subsequent replacement without issue. The patient was discharged approximately 2 mo after the procedure after the management of his primary disease, during which time no further complications were noted. A month later, the patient passed away as a result of complications of primary disease while in hospice care.

DISCUSSION

When comparing the standard of care (PEG) to LJG, we can see advantages concerning the fistula tract. In a PEG, there is rapid obliteration of the fistula if the tube becomes dislodged, which allows for only a small window in which replacement of the tube may be possible. In these settings, repeat instrumentation or another procedure for enteral access may be required[17], in addition to possible complications of the gastric leak[18]. The LJG does not share this complication, due to the mucous layer surrounding the gastrostomy tube, as well as the maturation of the gastric tube to the skin. A feeding tube can be safely replaced without concern, or in certain circumstances may be removed and replaced

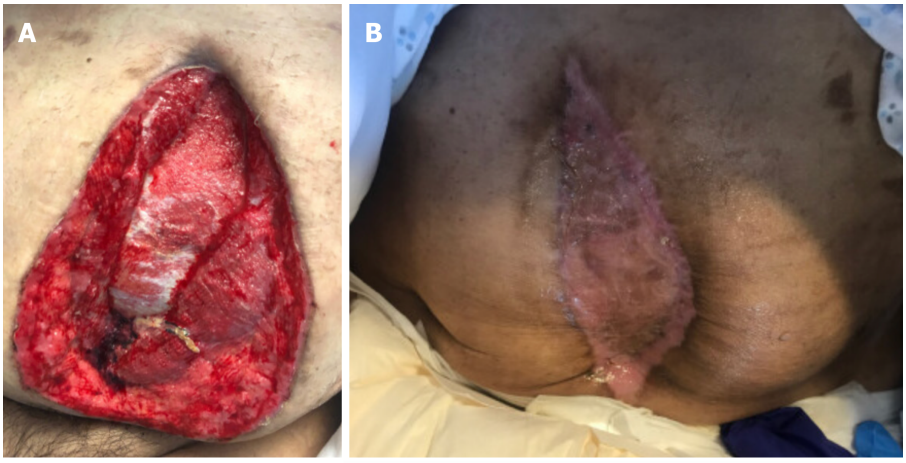

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Figure 4 Patient B's skin graft. A: Anterior abdominal wall view before skin grafting; B: Anterior abdominal wall view after skin grafting and appropriate healing, to illustrate abdominal wall anatomy.

freely and intermittently when feeding is needed. Additionally, this type of gastrostomy is performed *via* an objectively easy and reproducible procedure with few steps. We draw reference to the described cases above, both performed almost entirely by surgical residents and in an identical fashion. Even in the case of patient A, with prior intra-abdominal surgery as well as abdominal wall surgery, the procedure was performed with no significant adjustments. Several modifications to the original technique exist; in our cases we utilized trans-fascial anchoring sutures to the base of the gastric tube. This serves to relieve any tension on the gastric tube, increasing the surface area of anterior abdominal wall adherence. Another modification is the use of a port site as the site of the gastrostomy, limiting additional incisions. In earlier techniques of LJG, the gastric tube was created with the base of the gastric tube near the lesser curvature, in contrast to the modification used in the presented case where the base was at the greater curvature (Figure 3). This simple but strategic modification described in our cases allows for preservation of the blood supply of the gastric tube by the gastro-epiploic vessels, as well as allows for more desirable positioning of the gastrostomy lateral to the midline with an exit through the rectus muscles. The fixation of the exteriorized gastrostomy to the skin, akin to the maturation of an ostomy, is not performed in surgical gastrostomies. This creates a definitive track that leads to the permanence and longevity of the LJG. The gastrostomy creation not only spares the need for a constant indwelling catheter but also provides continence as it exits through the rectus abdominis[12], with a sphincteric mechanism *via* the rectus muscles preventing reflux or incontinence[14]. This configuration may be advantageous in the population of patients with disorders such as seizures or cerebral palsy. Compared to PEG which lacks an anti-reflux mechanism, the sphincter created during the LJG may be more preventative against complications of convulsive patterns including reflux, leakage from the stoma, and stomal prolapse[15].

This systematic review was performed with a focus on technical ease and reproducibility of procedure, resistance to complications such as tube dislodgement, and evaluating the use of the LJG as a permanent or long-term feeding access option as it compares to the alternatives. In terms of operative times, most of the studies published share a very similar range and mean duration; with an average time of 35.3 min for all the 43 patients with their times documented. We propose three main reasons for the difference between these studies and the 2 case reports of our own (with an average operating time of 81 min). One is likely due to the procedures in our studies being performed almost entirely by residents, with a large focus on education and laparoscopic skill development. The other proposed reason is that in "Patient B", the procedure was initially delayed by a transient intolerance to pneumoperitoneum, after which, following optimization by anesthesia, we were able to proceed. This delay was factoring into the total operative time which is a series of only 2 patients may lead to a greatly extended average operating time. The third proposed reason for time discrepancies relates to the technique used; in our two described cases, we employed the use of intracorporeal anchoring sutures to affix the base of the gastric tube to the anterior abdominal wall - an optional modification to the LJG to provide additional support, not performed in other reports. With regards to use as a long-term option for feeding access, there exists an objective theoretical advantage for LJG. By the creation of a gastric tube and maturation to the skin, a technique unique to the JG/LJG, there cannot be spontaneous closure of the fistula, making this ideal for long-term, palliative, or permanent enteral access. This systematic review looked at the documented MUTs of LJG (Table 2) to establish its role in longevity. This proved difficult, since the LJG by these benefits, was used quite extensively in populations consisting of terminal patients, or patients residing in nursing homes with expectedly poor follow-up.

We acknowledge that the goals of this paper are to demonstrate characteristics of the laparoscopic Janeway specifically, but we believe that with regards to MUT post-procedure, we may be able to utilize data from the subset of OJG analyzed (Table 3), as the result of these procedures is the same regarding gastrostomy use. The average MUT between the LJG and OJG groups is approximately 4 mo, however these results obtained do not reflect the true permanence of this procedure. In the above studies we had no documented cases of reversal of the gastrostomy, and due to the essential nature of the indications for this procedure, we can extrapolate that the LJG likely lasted the intended length of time: the rest of the respective patients' lives. Of the 56 patients who underwent LJG in the analyzed articles, we note 13 total complications and 0 mortalities related to the procedure; reported mortalities were related to the medical condition itself as seen in our case series. We attempted to stratify these into major and minor complications. The only identified major complication occurred in 1 patient in this series, in the case of Ritz *et al*[12], which documents a case of stomal necrosis, attributed by the authors to the creation of a gastric tube that was too small. This case necessitated surgical revision and conversion to a Witzel gastrostomy, with the remainder of the post-operative course unremarkable. With regards to the minor complications, we note 8 total cases of skin irritation[12,14,19] all of which were self-limiting. Tous Romero *et al*[19] documented one case in which a stoma granuloma formed, and this did not affect the functioning of the gastrostomy nor the quality of patient life, demonstrating the preferable complication profile for the LJG.

A significant complication of most gastrostomy procedures is tube dislodgement. This highlights possibly the most desirable feature of the LJG, that tube dislodgement at any time post-operatively does not cause any complication and poses no significant risks to the patient. This benefit is not only theoretical; we see it in clinical practice. In Raakow *et al*[14], the authors had the gastrostomy tubes removed from the gastrostomy intermittently, beginning on postoperative days 10-14 without any complications related to removal or reinsertion. We saw this in our case of "Patient B" in the presented clinical case, where the patient himself removed the gastrostomy tube on postoperative days 11, 18, 48, and 61, with no concerning sequelae following bedside replacement. There may have been a need for reoperation, especially with the first two removals, had the procedure been any other gastrostomy than an LJG. Comparing the complication profile of the LJG to that of a PEG, Ritz *et al*[12] demonstrate that PEG has a complication rate up to 30% (minor) and 9% (major) with a 1%-2% mortality. This is further corroborated by Rahnemai-Azar *et al*[6] in a comprehensive literature review, which identifies 8 minor and 6 major complications associated with PEG. The dislodgement of the PEG tube is seen to occur in approximately 12.8% of patients, with management strategies including replacement or new PEG or surgical gastrostomy creation. Other major complications of PEG described that may be mitigated by the use of LJG include buried bumper syndrome, not using the classic PEG tube, and hollow viscus inadvertent injury, as direct visualization is possible[6].

Comparing LJG to other surgical gastrostomies, data from the existing literature advocates a more benign complication profile as compared to the other surgical alternatives. Ritz *et al*[12] compared complications of open Witzel, Stamm, Kader, and Janeway gastrostomy. The OJG had a complication rate of 0%-25%, with a mortality rate of 0%-11%, favorable to that of the other open surgical alternatives with a collective complication rate of 13%-42% and a mortality rate of 10%-23%. These rates in OJG were then compared to those of LJG, with LJG having a 0%-6% complication rate and 0% mortality[20,21]. For completion, laparoscopic Kader gastrostomy was also compared to the rates for LJG, with complication rates of 6%-9% and mortality rate of 0%-5%, illustrating the preferable results of the LJG. Raakow *et al*[14] further supplemented these results by noting that when the Janeway technique is applied, the risks of developing postoperative leakage are notably decreased (approximate 0%-1%) when compared to approximately 9% as seen in the other surgical gastrostomies[14]. Abdel-Lah *et al*[16] in a more recent study, compared the LJG directly to the OJG. However, no statistical differences were noted given the variety of the population and the lack of specific primary outcomes. This highlights the need for more studies to investigate these differences.

LIMITATIONS

We identify several limitations in this literature review. Firstly, the majority of the studies analyzed had a relatively low sample size, with a total of 158 patients analyzed (56 patients with LJG and 102 with OJG). Another limitation is that there are no randomized controlled trials available in the literature that compares LJG to other gastrostomy creation techniques. This is the gold standard for inferring causation from correlation, and without this type of study we acknowledge less strength of the presented literature. In addition, there is limited research on the use of LJG, as evidenced by the small number of articles retrieved with broad search terms. Another limitation of this review is that many of the indications for LJG described in the literature are for palliative purposes with a large cohort of patients having advanced-stage cancers. This confounds the investigated MUT of the gastrostomy tube, which may have been longer had the patients not had poor prognoses. This limits the ability of this study for long-term analysis. Lastly, we noted that scarce recent data has been published on JGs, as evidenced by including articles published over 20 - 40 years ago. A proposed reason for this chronology is that

surgical gastrostomies have been seldom performed in recent years due to the popularity of the PEG and indicates strong potential for future studies where recent data is lacking.

CONCLUSION

The LJG is a viable technique for the creation of permanent or long-term enteral access, by its simple, reproducible technique and desirable complication profile, especially with for tube removal or dislodgement. As seen in many of the cases reviewed, this can be performed by advanced laparoscopists, surgical residents, and general surgeons without formal laparoscopic fellowship training. We acknowledge the data supporting PEG as a first-line feeding option, and advocate that the LJG should be strongly considered as a first-line option in specific patient populations, those who require permanent enteral access who may be at risk of tube dislodgement or removal due to agitation or neurologic disease. Another role for LJG as a first-line option may be in the setting where PEG is infeasible, for example, in cases of advanced head and neck cancer, severe abdominal wall scarring, and inability to get transillumination, as seen in the cases reviewed. LJG also has a beneficial potential role as a second-line option should a PEG be unable to be performed or unsuccessful, for any sign of long-term feeding access. This literature review, besides describing the many advantages of this procedure, has made us aware of the need for further study and randomized controlled trials of this promising technique.

ARTICLE HIGHLIGHTS

Research background

LJG, when initially described, was used as one of the first-line enteral access options, and has since been replaced by the advent and popularity of PEG. The significance of this study is that it demonstrates that the laparoscopic modification may be an acceptable first-line procedure for specific indications due to its longevity and ease of completion.

Research motivation

The main topics of this paper are that LJG may have more clinical relevance than previously considered. The problems this paper addresses is the complication rate including those caused due to dislodgement and tube removal with the PEG procedure. This procedure ameliorates these complications and may have a role in first-line access for specific indications.

Research objectives

The main objectives of this project was to describe cases of LJG as well as perform a systematic review of the available data as it relates to LJG for enteral access. We realized from this review, that LJG may serve as a viable alternative to PEG as a first-line option for enteral access in specific populations. The significance of this realization can result in lower morbidity and mortality as it relates to the complications of PEG dislodgements in specific patient populations.

Research methods

A systematic review was performed of all available data of LJG relating to use for enteral access. This data was analyzed by the reviewers to realize the objectives. To our knowledge, no large systematic reviews of LJG have been recently performed for this purpose.

Research results

Our findings describe relatively low rate of complications from LJG, largely as a result of the permanent gastrostomy tube formed in the procedure. We also note significant technical ease in completion of the procedure.

Research conclusions

This study proposes that LJG may be a viable alternative to PEG as a first-line procedure in specific patient populations.

This study describes the laparoscopic modification of Janeway gastrostomy and notes the technical ease and reproducibility.

Research perspectives

The direction for future research in this topic may include prospective studies and randomized controlled trials to determine true comparative data between LJG and PEG and other gastrostomy alternatives, and also to provide objective data to guide optimal patient selection.

FOOTNOTES

Author contributions: Murray-Ramcharan M conceptualized research study and both Murray-Ramcharan M and Fonseca Mora M designed the research study; Murray-Ramcharan M and Fonseca Mora M performed the research; Gattorno F and Andrade J contributed analytic tools and editing; Murray-Ramcharan M and Fonseca Mora M analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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CASE REPORT

Tracheoesophageal fistulas in coronavirus disease 2019 pandemic: A case report

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Abstract

BACKGROUND

Tracheoesophageal fistulas (TEFs) can be described as a pathological communication between the trachea and the esophagus. According to their origin, they may be classified as benign or malignant. Benign TEFs occur mostly as a consequence of prolonged mechanical ventilation, particularly among patients exposed to endotracheal cuff overinflation. During the severe acute respiratory syndrome coronavirus 2 virus pandemic, the amount of patients requiring prolonged ventilation rose, which in turn increased the incidence of TEFs.

CASE SUMMARY

We report the cases of 14 patients with different comorbidities such as being overweight, or having been diagnosed with diabetes mellitus or systemic hypertension. The most common symptoms on arrival were dyspnea and cough. In all cases, the diagnosis of TEFs was made through upper endoscopy. Depending on the location and size of each fistula, either endoscopic or surgical treatment was provided. Eight patients were treated endoscopically. Successful closure of the defect was achieved through over the scope clips in two patients, while three of them required endoscopic metal stenting. A hemoclip was used to successfully treat one patient, and it was used temporarily for another patient pended surgery. Surgical treatment was performed in patients with failed endoscopic management, leading to successful defect correction. Two patients died before receiving corrective treatment and four died later on in their clinical course due to infectious complications.

CONCLUSION

The incidence of TEFs increased during the coronavirus disease 2019 pandemic (from 0.5% to 1.5%). We believe that endoscopic treatment should be considered as an option for this group of patients, since evidence reported in the literature is still a growing area. Therefore, we propose an algorithm to lead intervention in

patients presenting with TEFs due to prolonged intubation.

Key Words: Tracheoesophageal fistula; COVID-19; Endoscopy therapy; Gastroenterology therapy; Case report

Core Tip: Due to the significant increase of tracheoesophageal fistulas in the context of severe coronavirus disease 2019 (COVID-19) pneumonia, and the high frequency of risk factors in patients with COVID-19, we recommend early identification and correction of these factors, such as frequent measurement of the cuff pressure and, if possible, periodic evaluation of the tracheal mucosa with bronchoscopy to identify early precursor lesions of tracheoesophageal fistula. Regarding treatment, provide initial endoscopic management until optimal conditions for surgical management are reached. Endoscopic management should be selected according to the size and location of the fistula.

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INTRODUCTION

Tracheoesophageal fistulas (TEFs) are defined as abnormal communications between the esophagus and the trachea or bronchi, leading to the passage of oral and gastric secretions into the respiratory tract[1]. TEFs can be classified into two main categories: Congenital or acquired. The congenital form is frequently associated with type C esophageal atresia (85%), presenting in an isolated manner in 4% of cases. Characteristically, clinical manifestations of this condition develop early in life[2-4]. On the other hand, acquired TEFs mainly affect adults and are most frequently found in the cervicothoracic junction. TEFs can be malignant or benign. Each type constitutes approximately half of the acquired cases[4].

Malignant TEFs are a catastrophic complication of invasive neoplasms of the esophagus (squamous cell carcinoma), trachea, lung, or mediastinum[4-6]. On the other hand, benign fistulas mainly develop due to prolonged mechanical ventilation (through an endotracheal tube or tracheostomy); blunt trauma to the neck and chest; traumatic or surgical injury of the esophagus; granulomatous mediastinal infections; previous esophageal stents, or ingestion of foreign bodies/corrosives[5]. In patients undergoing invasive mechanical ventilation, some of the risk factors for TEFs include prolonged intubation, endotracheal cuff overinflation, excessive movement of the endotracheal tube (prone positioning), hypotension, diabetes mellitus, previous respiratory tract infections, use of steroids, and requiring nasogastric tube feeding, among others[7,8].

The most common clinical presentation of TEFs includes respiratory distress, dysphagia, cough after swallowing (ONO sign), malnutrition, and recurrent pulmonary infections. The severity of symptoms largely depends on their size and location[8,9]. A diagnosis should be made by combining characteristic findings on thoracic imaging (esophagogram and chest tomography with 3D reconstruction) and those on endoscopic studies such as bronchoscopy and upper endoscopy. These studies are also essential when planning the best treatment option for each patient[1,8,10,11].

The mean survival reported for patients with TEFs is less than 3 mo from the time of diagnosis. As such, adequate treatment should include an immediate multidisciplinary approach, including specialists in critical care, interventional pulmonology, gastroenterology, and thoracic surgery. Currently, there are few case reports regarding TEFs due to prolonged intubation in patients with coronavirus disease 2019 (COVID-19)[12-16]. We herein present a case series on patients with COVID-19 who develop TEFs and discuss diagnostic and therapeutic approaches.

CASE PRESENTATION

Chief complaints

Before creating this case series, we obtained informed consent from each patient or their legal guardians. We included patients who were admitted to a university hospital in the city of Bogotá, Colombia in the period between November 2020 and December 2021. We identified 14 adult patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia who developed TEFs as a complication

of prolonged mechanical ventilation.

We present the sociodemographic variables of the patients and relevant information on their past medical histories in Table 1. The average age was 53.5 years (range 38-72 years). Half of the sample was composed by men. Comorbidities were found in 85.7% of the patients, with the most frequent being obesity/overweight, diabetes mellitus, and systemic hypertension.

History of present illness

The clinical characteristics of the patients are shown in Table 2. The most common symptoms, which lead all patients to attend the emergency room, were cough and dyspnea. All of the subjects were diagnosed with severe pneumonia due to COVID-19. At least 64.2% presented with septic shock, requiring vasoactive support. All patients required invasive mechanical ventilation for more than 14 d. Acute respiratory distress syndrome (ARDS) was documented in 13 patients, and this variable was no available for assessment in one patient. All patients were treated with a steroid (dexamethasone: 6 mg s.c., q.d. for 10 d), and the steroid was prematurely stopped in one patient due to diabetic ketoacidosis during treatment. All patients received enteral nutrition through nasoenteral tubes.

The pressure of the endotracheal cuff was measured in only two patients (14.2%), being greater than 35 cmH_2O in both cases. TEFs were documented by endoscopic study of the upper digestive tract (100%) and in some cases with three-dimensional reconstruction of neck computed tomography (71.4%). All TEFs were found in the proximal esophagus, with an average distance of 16.7 cm from the dental arch, and the average diameter was 18.2 mm (range 3 mm-40 mm) (Figure 1).

All of the patients had bacterial infectious complications, including tracheitis (21.4%), pneumonia (64.2%), and bacteremia (21.4%). Therefore, they required treatment with broad-spectrum antibiotics leading to *Clostridioides difficile* infection in 14.2% of the sample. Six patients developed terminal acute kidney injury requiring renal replacement therapy. For the closure of TEFs, eight patients were taken to temporary or definitive endoscopic treatment: Four needed over the scope (OTS) clips, achieving successful endoscopic closure in two. Clip placement failed in one of the patients due to tissue fibrosis; a recurring defect was documented in another patient. Three patients received temporary management with a fully coated metallic stent (SEMS), managing to completely cover the defect. Hemoclips (TTS endoclips) were used in two patients. In one patient, with a 3 mm TEF, adequate closure of the defect was achieved; while in another patient, temporary reduction in diameter was achieved, allowing further management with an OTS clip (Figure 1). In six patients, a surgical approach was indicated given the location and size of the fistula. Surgical management was also provided to the patient with failure to therapy with the OTS clip, achieving successful correction of the defect. On follow-up, recurrence of TEFs was observed in only one patient treated with an OTS clip, and an increase in the size of the fistula was detected, for which surgical therapy was considered, successfully closing the defect. Despite the efforts made, 42.8% (6/14) died due to infectious complications, with two patients dying before receiving surgical management.

History of past illness

Comorbidities were found in 85.7% of the patients, with the most frequent being obesity/overweight (71.4%), diabetes mellitus (42.8%), and systemic hypertension (42.8%).

Physical examination

Half of the sample was composed by women with an average weight of 72.4 kg (body mass index [BMI] 27.4). The men had an average weight of 82 kg (BMI 26.6). The pressure of the endotracheal cuff was measured in only two patients (14.2%), being greater than 35 cmH_2O in both cases.

Imaging examinations

Three dimensional reconstruction of neck computed tomography was performed in 13 patients (92.8%), identifying the presence of a fistula in 71.4%. At the time of diagnosis, all patients were on invasive mechanical ventilation, so esophagogram was not performed in any of them.

FINAL DIAGNOSIS

TEFs were documented by endoscopic study of the upper digestive tract (100%) and in some cases with three-dimensional reconstruction of neck computed tomography (71.4%). All TEFs were found in the proximal esophagus, with an average distance of 16.7 cm from the dental arch, and the average diameter was 18.2 mm (range 3-40 mm) (Figure 1).

TREATMENT

For the closure of TEFs, eight patients were taken to temporary or definitive endoscopic treatment: Four

Table 1 Characteristics of patients with tracheoesofageal fistulas in 2020-2021

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total, *n* (%)
Age (years)	60	58	72	52	46	63	56	46	41	61	49	39	69	38	
Sex	M	F	M	F	F	F	F	F	M	M	M	M	M	F	
BMI	25.1	34.3	23.9	28.6	32	19.1	28	27	26	29.5	23	32	27.1	23.4	
Past medical history															
Diabetes mellitus	-	X	-	-	X	-	X	X	-	-	-	X	X	-	6 (42.8)
Systemic hypertension	-	-	X	-	-	X	X	X	-	-	-	X	X	-	6 (42.8)
Obesity/Overweight	X	X	-	X	X	-	X	X	X	X	-	X	X	-	10 (71.4)
Other	-	-	PC	-	-	H	-	-	H	AF	-	-	-	-	

BMI: Body mass index; M: Male F: Female BMI: Body mass index PC: Prostate cancer; H: Hypothyroidism AF: Atrial fibrillation.

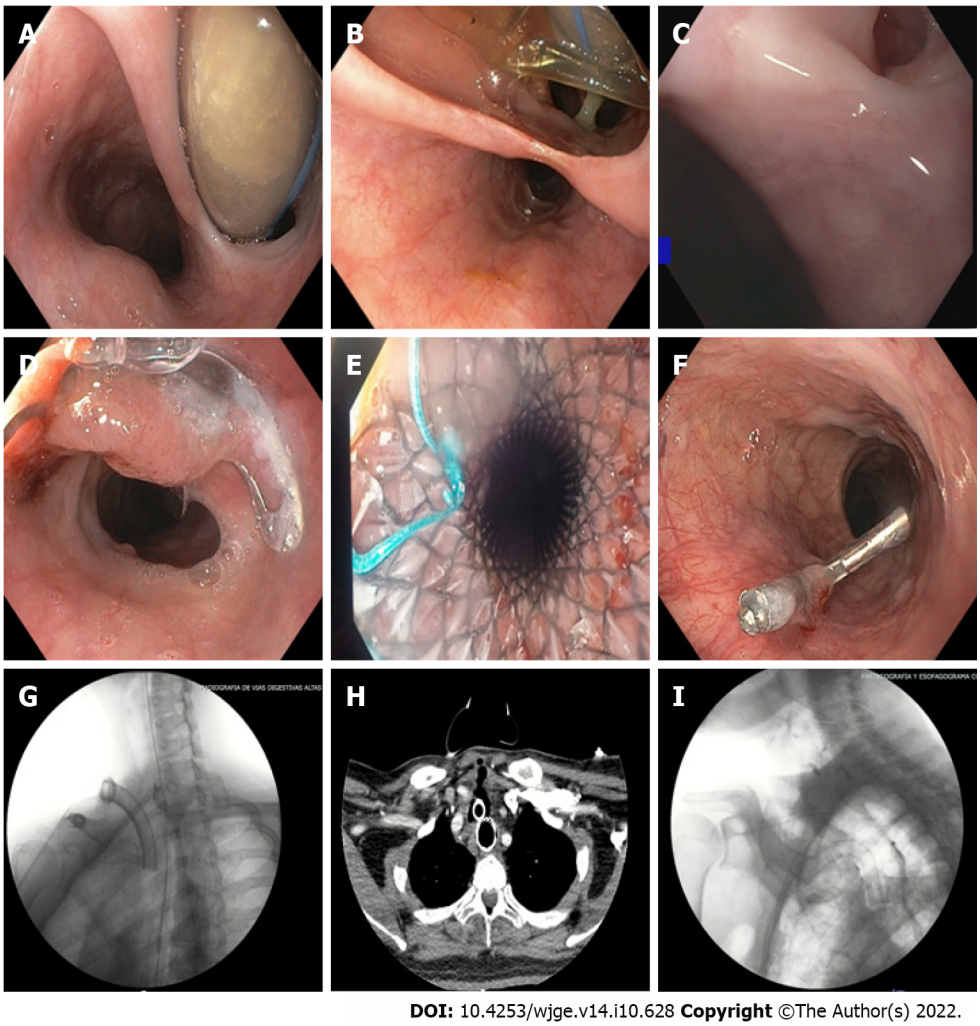

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Figure 1 Tracheoesophageal fistulas: Diagnosis and management. A: 20 mm tracheoesophageal fistula (TEF); B: 30 mm TEF; C: 3 mm TEF; D: Over the scope (OTS) clip closure (video 1); E: Closure with a partially coated self-expanding metal stent; F: Closure with a through-the-scope clip (TTS) endoclip; G: Esophagogram without leakage after OTS clip therapy; H: Axial computerized tomography showing closure of TEF with a fully covered SEMS; I: Esophagogram displaying TEF closure through TTS endoclips, with aspiration due to deglutition disorder. (Further pictures and video may be found as Supplementary material).

needed OTS clips, achieving successful endoscopic closure in two (video 1). Clip placement failed in one of the patients due to tissue fibrosis; a recurring defect was documented in another patient. Three patients received temporary management with a fully coated metallic stent (SEMS), managing to completely cover the defect. Hemoclips (TTS endoclips) were used in two patients. In one patient, with a

Table 2 Characteristics of patients with tracheoesophageal fistula in 2020-2021

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total, *n* (%)
Reason for consultation															
Fever	X	-	X	X	X	X	-	X	X	-	X	X	X	-	10 (71.4)
Cough	X	X	X	X	X	X	X	X	X	X	X	X	X	X	14 (100)
Dyspnea	X	X	X	X	X	X	X	X	X	X	X	X	X	X	14 (100)
Clinical findings															
Viral pneumonia SARS CoV2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	14 (100)
SOFA	2	6	ND	4	8	ND	ND	10	ND	ND	ND	ND	6	ND	
Clinical course															
Invasive mechanical ventilation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	14 (100)
ARDS	X	X	ND	X	X	X	X	X	X	X	X	X	X	X	
Vasoactive	X	X	ND	X	X	X	ND	X	X	X	ND	ND	X	ND	
Shock	X	X	ND	X	X	X	ND	X	X	X	ND	ND	X	ND	
Steroids	X	X	X	X	X	X	X	X	X	X	X	X	X	X	14 (100)
Dispositivo vía esofagica	X	X	X	X	X	X	X	X	X	X	X	X	X	X	14 (100)
Cuff pressure measurement	-	-	-	X	-	-	-	-	X	-	-	-	-	-	2 (14.2)
Tracheostomy	X	X	-	X	-	-	X	-	X	X	X	X	-	X	9 (64.2)
Gastrostomy	X	-	-	X	-	X	X	-	X	X	X	X	-	X	9 (64.2)
Diagnosis															
Upper gastrointestinal endoscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	14 (100)
Axial computed tomography of the neck	X	X	X	X	X	X	N	X	-	N	X	X	N	X	13 (92.8)
Complications															
Tracheitis	X	-	-	-	-	-	-	-	-	-	-	X	X	-	3 (21.4)
Pneumonia	-	-	X	X	X	X	X	X	X	X	-	-	-	X	9 (64.2)
Bacteremia	-	X	-	-	-	-	-	-	-	-	X	-	-	X	3 (21.4)
Clostridioidal infection	-	-	X	-	-	-	-	-	-	-	-	-	-	X	2 (14.2)
Acute kidney injury	-	X	-	-	-	-	-	X	X	X	X	-	X	-	6 (42.8)
Treatment															
OTS clip	X	-	X	X	-	-	X	-	-	-	-	-	-	-	4 (28.5)
TTS endoclip	-	-	-	-	-	-	X	-	-	X	-	-	-	-	2 (14.2)
Self-expanding metallic stent	-	X	-	-	-	-	-	X	-	-	-	X	-	-	3 (21.4)
Surgery	X	-	-	X	-	X	-	-	X	-	X	X	-	X	7 (50)

TTS: Through-the-scope clip; OTS: Over-the-scope clip; ND: No data; SOFA: Sepsis organ failure assessment; ARDS: Acute respiratory distress syndrome; N: No fistula detected.

3mm TEF, adequate closure of the defect was achieved, while in another patient, temporary reduction in diameter was achieved, allowing further management with an OTS clip (Figure 1). In six patients, a surgical approach was indicated given the location and size of the fistula. Surgical management was also provided to the patient with failure to therapy with the OTS clip, achieving successful correction of the defect. On follow-up, recurrence of TEFs was observed in only one patient treated with the OTS clip, and an increase in the size of the fistula was detected, for which surgical therapy was considered, successfully closing the defect.

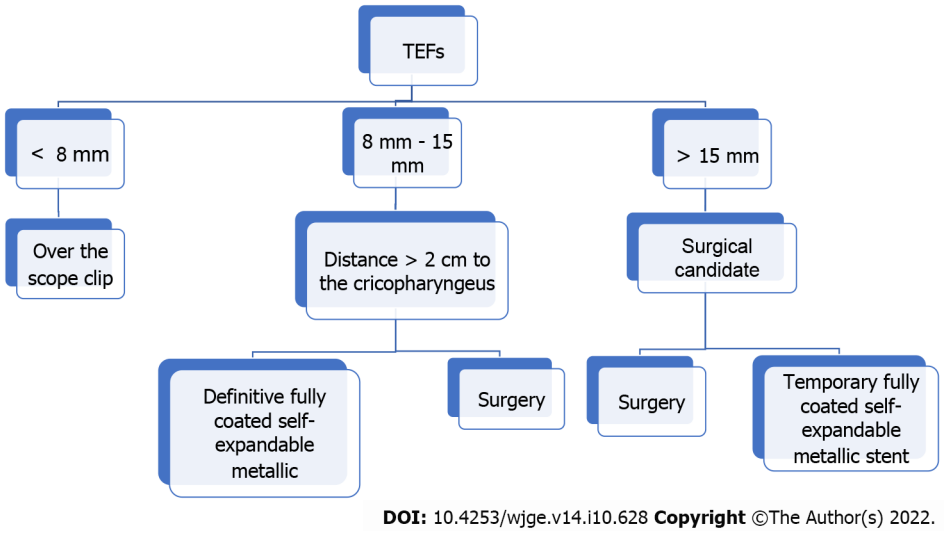

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Figure 2 Suggested treatment algorithm.

OUTCOME AND FOLLOW-UP

Despite the efforts made, 42.8% (6/14) of the patients died due to infectious complications, with two patients dying before receiving surgical management.

DISCUSSION

Acquired TEFs are a rare clinical entity, with incidence rates approaching 0.5%. Up to 75% of cases are due to trauma related to endotracheal cuff overinflation or prolonged mechanical ventilation[4,8,17]. The pressure exerted by the endotracheal tube cuff erodes the tracheal mucosa, leading to ischemic destruction of the tracheal cartilage, which creates a communication with the esophageal wall[4,8].

The current health situation, due to the SARS-CoV-2 pandemic, which significantly increased cases of severe pneumonia and ARDS, led to a parallel increase in TEFs associated with prolonged endotracheal intubation. We found that 14 out of 894 patients undergoing mechanical ventilation for severe COVID-19 pneumonia, developed TEFs (incidence 1.56%). In most patients, several risk factors were simultaneously found; these included prolonged mechanical ventilation, hypotension, steroid use, diabetes mellitus, obesity, and excessive movement of the endotracheal tube due to frequent position changes (supine-prone)[18]. We hypothesize that monitoring of the endotracheal cuff pressure was insufficient, possibly due to overcrowding in critical care units, as well as the exhaustion, anxiety, and depression developed by healthcare workers during the pandemic[19,20,21,22].

Spontaneous closure of TEFs is rare, and therefore requires the use of different treatment approaches, including endoscopic and surgical options[4,7,23]. Among the endoscopic options is the use of fully coated metallic stents (SEMS), OTS clips, TTS endoclips, and suture systems among others[24-27]. These procedures have allowed for high success rates (73%-83%) regarding closure of perforations, leaks, and gastrointestinal fistulas[28]. However, due to a low incidence of TEFs, no consensus guidelines on the management of this entity currently exist, particularly concerning patients with SARS-CoV-2 infection. It has been reported that mechanical ventilation increases the risk for suture dehiscence. Furthermore, comorbidities and the critical condition of patients with severe COVID-19 pneumonia usually lead to deferral of surgical procedures until after mechanical ventilation withdrawal. This is why considering endoscopic interventions as initial management in critically ill patients with tracheoesophageal fistula associated with mechanical ventilation due to COVID-19 should be sought.

We present a treatment algorithm for this group of patients in Figure 2. Our approach is determined by the size and location of the fistula, using OTS clips for defects below the size of 8 mm. For lesions between 8 and 15 mm, we suggest to use SEMS as long as the fistula is more than 2 cm distal to the cricopharyngeus where the stent can be properly fixed. In lesions larger than 15 mm, we propose upfront surgical treatment, as well as when the fistulas are less than 2 cm from the cricopharyngeus (because at this distance the stent may lead to foreign body sensation). When the patient is not a good surgical candidate and has lesions larger than 15 mm located more than 2 cm away from the cricopharyngeus, a fully SEMS can be placed as bridging therapy until the patient becomes stable and in better condition for surgical treatment. Although we have a small sample size, to the best of our knowledge, this is the first study to illustrate the management of this type of patients in the context of the coronavirus pandemic.

CONCLUSION

Due to the significant increase in diagnosis of TEFs in patients with severe pneumonia due to COVID-19, and the high frequency of risk factors for TEFs in these patients, we recommend early identification and prevention of these conditions, in addition to frequent measurement of the endotracheal cuff pressure. If possible, we recommend periodic evaluation of the tracheal mucosa by bronchoscopy to identify early lesions that could lead to the development of TEFs. Regarding treatment, we suggest providing initial endoscopic management in small fistulas (below 15 mm) or until optimal conditions for surgical management are met (if larger than 15 mm). Definitive endoscopic treatment may be offered according to the size and location of the fistula.

FOOTNOTES

Author contributions: Gomez M was responsible for the revision of the manuscript for important intellectual content; Gallego D and Ruiz O reviewed the literature and contributed to manuscript drafting; all authors were the patient's gastroenterologists; all authors issued final approval for the version to be submitted.

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CASE REPORT

Hemostasis of massive bleeding from esophageal tumor: A case report

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Abstract

BACKGROUND

Esophageal cancer is a common type of cancer and serious bleeding from esophageal tumors can occur in routine clinical practice. The arrest of bleeding from esophageal tumor is not a trivial task, which can sometimes require non-standard solutions. We report a case of successful hemostasis of massive bleeding from esophageal tumor performed by a novel two-balloon catheter inserted endoscopically, with a local hemostatic treatment applied.

CASE SUMMARY

A 36-years old male patient with advanced esophageal cancer developed bleeding from the tumor following endoscopic stenting with a self-expanding metal stent. Due to the ineffectiveness of standard approaches, after a medical conference, the patient was treated with a novel method based on the use of a two-balloon catheter creating an isolated area in esophagus and locally dispersing hemostatic polysaccharide powder inside the isolated interior. Hemostasis was successful and subsequent endoscopic examination revealed the presence of organized clot and localized defect, which was coagulated in a planned manner.

CONCLUSION

The authors present a new catheter-based method of hemostasis of esophageal tumor bleeding.

Key Words: Esophageal cancer; Esophageal bleeding; Two-balloon catheter; Endoscopic hemostasis; Hemostatic polysaccharide powder; Case report

Core Tip: We describe a novel method of managing difficult-to-treat condition using an original device/catheter that we developed. Our experience of managing gastrointestinal and, in particular, esophageal bleeding suggests that treatment of such conditions is a major challenge with no readily available and reliably working solutions. Success depends on multiple factors, all subject to limitation of time available for decision-making and application of treatment methods. A major advantage of our method is its ease of use and ability to be deployed by physicians of all levels and in all hospital settings. We believe that our method can help save many lives.

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INTRODUCTION

Various stages of dysphagia are common complications of esophageal cancer. Stenting of esophageal tumors is a standard method of treatment and palliative care. Placement of a self-expandable metal stent is required, on the one hand to facilitate oral nutrition and on the other hand as the first standard step of treatment pre-empting neoadjuvant chemotherapy with brachytherapy[1,2]. At the same time, placement of a stent can lead to the development of various complications, the frequency of which can reach up to 50%[3]. The most common are esophageal perforation, fistula, stent migration, and bleeding [4,5]. The incidence of bleeding after stenting is not high and varies from 1% to 12%[6,7]. However, the volume of bleeding if it occurs is often massive and is associated with high mortality[6,7]. Due to the fact that this complication is rare, and its course is extremely aggressive, the experience of managing this group of patients is limited. The recommendations are nonsystematic in nature and one should be prepared for various scenarios, from the application of various hemostatic remedies and transfusion of blood components to angiographic methods to stop the bleeding. The unfavorable outcome of this complication can be caused by a stent itself that interferes with verification of the source of bleeding, by pathological hypervascularization of a tumor, rich blood supply of the esophagus, including from esophageal arteries stemming from the descending aorta, and by a limited amount of time available to help a patient[6-9].

Analysis of the literature suggests that time is the main factor in the unsatisfactory result of trying to achieve hemostasis during the first wave of bleeding. The time spent on patient admission and delays in identifying the source of bleeding, trying various options of endoscopic hemostasis, switching to endovascular methods, all negatively affect the outcome of treatment. To counter this, a method has been developed that consists of isolating the source of bleeding, in this case the part of the esophagus with a tumor, from other parts of the gastrointestinal tract, with the possibility of delivering hemostatic agents into it while maintaining the connectivity between the parts of esophagus proximal and distal to the isolated region. The latter feature enables concurrent and continuous drainage of the proximal part and administration of solutions and enteral nutrition. This approach achieves several important effects. First, it allows one to mechanically create an isolated area with high pressure in which blood, clots, and coagulation factors facilitate hemostasis. Second, it enables localized delivery of hemostatic agents such as polysaccharide hemostatic powders. Third, by maintaining functional connectivity of the gastrointestinal tract, the method allows both for essential nutritional support and provision of fluids, and for sufficient exposure time to achieve hemostasis.

CASE PRESENTATION

Chief complaints

Vomiting with blood, melena, weakness, an episode of loss of consciousness.

History of present illness

A 36-year-old male patient was admitted on an emergency basis on November 14, 2021, with manifestation of gastrointestinal bleeding. At the time of admission, the degree of blood loss, according to the changes in the level of hemoglobin, erythrocytes and hematocrit, was assessed as moderate.

History of past illness

When collecting an anamnesis, it was established that for the first time the dysphagia was observed in

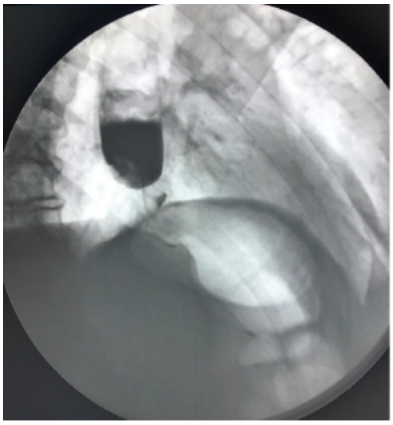

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Figure 1 X-ray of esophagus revealing a filling defect.

September 2021. An X-ray investigation performed at the time revealed changes characteristic of a tumor of the gastroesophageal junction (Figure 1). The patient categorically refused further examination and treatment and was discharged. Later he was followed up at the oncology clinic, and on October 29 diagnosed with cancer of gastroesophageal junction, type II according to Siewert classification, stage IVB, Grade 2, dMMR/MSI-h-negative, HER2-negative adenocarcinoma. Concomitant diseases: obesity class III, essential hypertension. On November 10, endoscopic stenting of esophagus was performed to resolve dysphagia. The patient was discharged on November 13, 2021.

Personal and family history

There was no personal and family history of cancer.

Physical examination

At the time of admission, blood pressure was 80/40 mmHg and heart rate was 114 beats/min.

Laboratory examinations

Blood analysis demonstrated high volume of loss, with erythrocyte count 2.1 mln cells/uL, hemoglobin 79 g/L, and hematocrit 31.0%.

Imaging examinations

Endoscopic examination revealed that there was ongoing bleeding from under the partially covered esophageal stent (Figure 2). It was however not possible to clearly establish the localization of the source of bleeding.

MULTIDISCIPLINARY EXPERT CONSULTATION

Given the severity and urgency of situation, a multidisciplinary meeting was held, which included surgeons, endoscopists and anesthesiologists.

FINAL DIAGNOSIS

Cancer of the gastroesophageal junction, type II according to Siewert classification, stage IVB, Grade 2, dMMR/MSI-h-negative, HER2-negative adenocarcinoma. Complications: severe esophageal bleeding. Concomitant diseases: obesity class III and essential hypertension.

TREATMENT

Both standard intravenous hemostatic therapy and blood component transfusion were administered. An attempt to perform endoscopic hemostasis by electrocoagulation of the tumor failed to achieve positive results. It was decided that due to the impossibility of achieving hemostasis using standard methods and further deteriorating condition of the patient, it was advisable, according to vital indications, to use the isolation method and locally introduce a polysaccharide powdered hemostatic

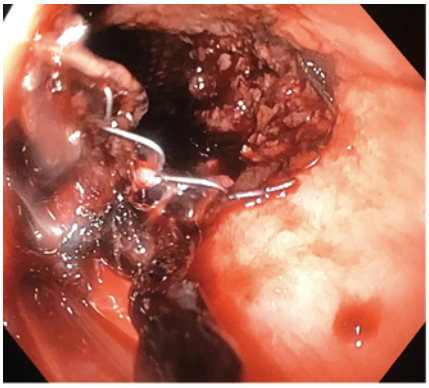

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Figure 2 Endoscopic view of bleeding with visualization of uncovered part of the stent. There were visible signs of tumor growth.

agent. The two-balloon catheter was inserted endoscopically into the stomach past the stent, so that the tumor site with the source of bleeding were located between the balloons. Balloons were inflated isolating the area of bleeding, and hemostatic powder was injected though the catheter opening located between the balloons and dispersed inside the isolated interior. The procedure stopped the bleeding, as demonstrated by normalization of hemodynamic parameters and absence of retrograde flow of blood through the main channel of the catheter. Over the next day, there was no sign of bleeding recurrence, which was supported by stable levels of hemoglobin and erythrocyte count. On November 15, the day after hemostasis, the catheter was removed, and repeated endoscopic procedure was performed in order to identify the source of bleeding and to reposition the esophageal stent. A 1.5-cm long defect with an organized clot was detected in the gastroesophageal junction (Figure 3). Argon plasma coagulation was performed after which the same stent was repositioned and fixed. Fluoroscopy performed on November 18 showed that stent's position was adequate, the contrast medium freely entered the stomach, and there were no streaks or signs of stent migration (Figure 4). No recurrence of bleeding was observed, and the patient was discharged on November 18 in adequate condition to continue treatment at the oncology clinic.

OUTCOME AND FOLLOW-UP

After 4 mo of follow-up on March 9, 2022, patient was hospitalized with recurrent dysphagia. Endoscopy of the upper part of the stent revealed tumor overgrowth and infiltration with stenosis of the esophagus. Endoscopic ablation with tumor coagulation and recanalization of the esophagus was performed successfully. Two days after the procedure, clinical signs of dysphagia disappeared, as confirmed by controlled esophageal fluoroscopy, and the patient was discharged.

DISCUSSION

Bleeding after stenting of esophageal cancer is a severe complication with a high rate of mortality. Most often it develops in the first 2 wk after manipulation[8,9]. The main reasons include mucosal trauma caused by the free uncovered part of the stent during active esophageal peristalsis and increased pressure on the wall of the organ at the time of its expansion by the stent, leading to necrotic changes [10]. Since the esophagus is well supplied with blood, the bleeding is often massive. The presence of a stent hampers identification of the source of bleeding, and prevents application of argon plasma coagulation, injection of adrenaline or clipping. Large number of collateral blood vessels and segmental type of blood supply of the esophagus are the reason why many authors recommend supplementing endoscopic approaches with endovascular methods of hemostasis, which nevertheless often fail to achieve the desired effect[8-10]. It is important to have a wide range of methods available for both identification and tackling of the source of bleeding. In clinical practice however, resources are often limited and implementation of extensive care is associated with loss of time, which in this case is critical. Presence of disseminated tumor and poor somatic status of a patient can also play an important role, limiting the surgeon's options.

The method of hemostatic treatment described here allows for localization of the source of bleeding by isolating it from other parts of the gastrointestinal tract. At the same time, it does not require identification of precise location of the site of bleeding. The method implements four hemostatic approaches: (1) Applying pressure on the submucosal vessels by the inflated balloons; (2) tamponade of the source

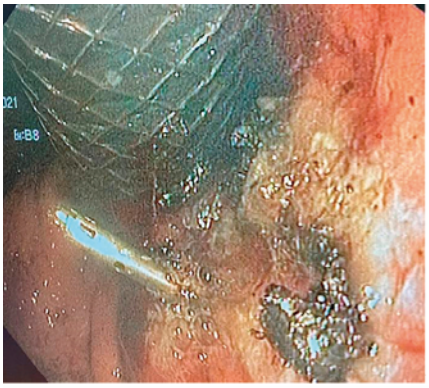

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Figure 3 View of a clot in the gastroesophageal junction after stent removal.

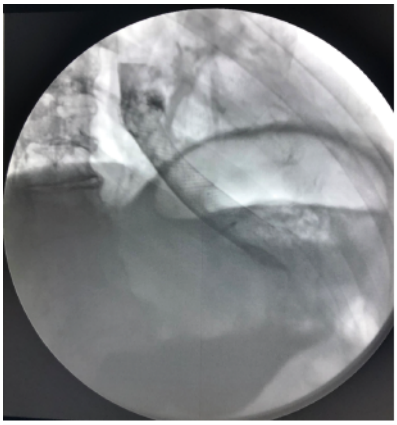

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Figure 4 X-ray of esophagus. Correct location of the stent in the gastroesophageal junction was visualized.

of bleeding by blood clots; (3) targeted delivery of hemostatic agents to the bleeding site; and (4) prevention of migration of hemostatic agents and blood clots to other parts of the gastrointestinal tract due to peristalsis. The latter prolongs exposure to hemostatic agents, which is enhanced by the ability of the two-balloon catheter used in the procedure to preserve connectivity of the gastrointestinal tract and to remain in place long enough to achieve the desired hemostatic effect.

CONCLUSION

Availability of a fast and simple method for stopping bleeding from a tumor in the esophageal lumen, which does not require a high level of specialist training, is easy to perform and that provides long-term hemostasis and ability to administer enteral nutrition and drain the upper part of the esophagus, will help save time and improve the quality of care for this group of patients. While the present case is focused on esophageal bleeding, the method proposed could be applied to treating bleeding in other parts of the gastrointestinal tract.

FOOTNOTES

Author contributions: Kashintsev AA, Anisimov SV, Granstrem OK, Kutumov EB, Nadeeva AA and Proutski V designed the study; Kashintsev AA, Rusanov DS, Antipova MV, Kokhanenko NY and Medvedev KV performed the study; Kashintsev AA, Anisimov SV, Granstrem OK, and Proutski V analyzed the results and wrote the manuscript; all authors have read and approve the final manuscript.

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CASE REPORT

Cronkhite-Canada syndrome: First case report from Egypt and North Africa

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Abstract

BACKGROUND

Gastrointestinal (GI) polyposis is a rare condition in GI diseases. To date about 500 cases of Cronkhite-Canada syndrome (CCS) have been reported worldwide.

CASE SUMMARY

We report a 60-year-old female patient who presented with dyspepsia, abdominal pain, and weight loss of 1-year duration. Her physical examination showed alopecia and onychodystrophy. Upper endoscopy revealed diffuse markedly thickened gastric mucosa involving the whole stomach with thickened gastric rugae and numerous polypoidal lesions. Histopathological examination showed marked hyperplasia of the foveolar glands with inflammatory cell infiltration. Endoscopic ultrasound showed a significantly hypertrophic mucosa and muscularis mucosa, while the submucosa and the muscularis propria were spared, favouring its benign nature. Colonoscopy showed multiple sessile polyps scattered at different parts of the colon. Histopathological examination revealed tubular adenomatous polyps with low-grade dysplasia. Differential diagnoses included CCS, Menterier disease (MD), other polyposis syndromes, lymphoma, amyloidosis, and gastric malignancies. The presence of alopecia, nail dystrophy, GI polyposis, markedly

thickened gastric mucosa and folds, abdominal pain, weight loss, and marked foveolar gland hyperplasia; all was in favour of CCS. Lymphoma was excluded due to sparing of the muscularis propria. The presence of colonic polyps and antral and duodenal infiltration, and the absence of hypoproteinaemia decreased the possibility for MD.

CONCLUSION
The patient was diagnosed as having CCS.

Key Words: Gastrointestinal polyposis; Thickened gastric mucosa; Cronkhite-Canada syndrome; Case report

Core Tip: Cronkhite-Canada syndrome (CCS) is a rare acquired polyposis with unknown aetiology. To date about 500 cases have been reported worldwide. We herein report an Egyptian patient with CCS. Most of CCS cases were reported from Japan, and to our knowledge, our case is the first case reported from Egypt and North Africa. Cases presenting with gastrointestinal (GI) polyposis and marked thickened gastric mucosa and folds represent challenging cases and diagnostic dilemmas. The diagnosis was based on history, physical examination, endoscopic findings, and histology. CCS is typically characterized by GI symptoms, such as diarrhea and skin changes (*e.g.*, alopecia, pigmentation, and nail dystrophy), while endoscopic features include diffuse polyps throughout the entire GIT, except for the esophagus. Pathological types of polyps in CCS mainly include inflammatory, hyperplastic, hamartomatous, and/or adenomatous polyps. CCS can be complicated by many diseases and has a malignant tendency with a high mortality rate. Till now, there has been no uniform standard treatment for CCS.

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INTRODUCTION

Cronkhite-Canada syndrome (CCS) is one of the rarest nonhereditary diseases[1], and its exact aetiology is still unknown[2], with around 500 cases having been described in the literature[3]. Most of CCS cases were reported from Japan, and to our knowledge, our case is the first case reported from Egypt and North Africa.

Patient with CCS usually presents with gastrointestinal (GI) symptoms such as abdominal pain, weight loss, and diarrhea, or with other symptoms such as onychodystrophy, alopecia, hyperpigmentation of the skin, and rarely vitiligo[4]. GI polyposis is the main endoscopic feature in CCS, which is commonly non-neoplastic and rather inflammatory, hyperplastic, hamartomatous, and/or adenomatous polyps in nature[5]. Moreover, some CCS cases may develop gastric and colorectal malignancies during the disease course[4].

CASE PRESENTATION

Chief complaints

A 60-year-old female patient presented with dyspepsia, abdominal pain, and weight loss of 1-year duration.

History of present illness

The patient denied other GI or anaemic symptoms. She was a non-smoker and did not drink alcohol.

History of past illness

The patient's past medical history was free apart from prolonged proton-pump inhibitor (PPI) intake.

Personal and family history

There was no family history of gastrointestinal polyposis or colorectal malignancy.

Physical examination

The physical examination was unremarkable apart from alopecia (Figure 1A) and onychodystrophy (Figure 1B).

Laboratory examinations

The patient's laboratory profile was within normal limits including a full complete blood picture (CBC), chemistry, serum albumin, serum calcium, urine analysis, antinuclear antibody (ANA), and IgG-4.

Imaging examinations

Oesophago-gastro-duodenoscopy (OGD) revealed diffuse markedly thickened gastric mucosa involving the whole stomach (fundus, body, and antrum), with thickened and tortuous gastric rugae, and numerous polypoidal lesions (3-10 mm in diameter), with a hyperaemic mucosa, and to a lesser extent down to the duodenal bulb and second part of the duodenum (Figure 2A and B). Multiple conventional biopsies were taken, and polypectomy was done for the large polyps for histopathological examination. Biopsies showed marked hyperplasia and cystic dilation of foveolar glands with inflammatory cell infiltration including eosinophils, hyperplastic polyps, chronic gastritis, and *Helicobacter pylori* (*H. pylori*) infection with no atypia or malignancy (Figure 3). IgG4-immunohistochemistry showed a very faintly positive signal.

Endoscopic ultrasound was done later and showed a significantly hypertrophic mucosa and muscularis mucosa, while the submucosa and the muscularis propria were spared, favouring its benign nature. Wall thickness was up to 8-10 mm (normal wall thickness is up to 4 mm) (Figure 2C).

Colonoscopy showed multiple variable-sized, sessile, and pedunculated polyps (~15), scattered at different parts of the colon. Snaring of the large polyps was done after submucosal injection (Figure 2D and E), and histopathological examination showed typical features of benign juvenile-like and hamartomatous polyps without dysplastic changes, while pathology of other polyps revealed tubular adenomatous polyps with low-grade dysplasia.

Both push enteroscopy and terminal ileoscopy showed no polyposis with a normal mucosa in the 3rd and 4th portions of the duodenum, the proximal jejunum, and the terminal ileum.

Computerized tomography (CT) scan of the abdomen & pelvis with oral and intravenous (IV) contrast revealed mild circumferential mural thickening of the gastric wall.

FINAL DIAGNOSIS

The patient was diagnosed as having CCS.

TREATMENT

The patient started a sequential therapy for *H. pylori* infection with complete eradication, followed by a proton pump inhibitor (40 mg once daily), prednisolone (30 mg/d), and mesalazine (500 mg QID) for 6 mo.

DISCUSSION

In our case, the following differential diagnoses were raised and discussed with our gastroenterologists: CCS, MD, other polyposis syndromes (such as familiar adenomatous polyposis, Gardner syndrome, juvenile polyposis, Peutz-Jeghers syndrome, and Turcot syndrome), lymphoma, amyloidosis, duodenal gastric heterotopia, and gastric malignancies.

The final diagnosis was based on the medical history, physical examination, endoscopic findings, and the histopathological examination. The presence of anomalies of ectodermal tissues (such as alopecia and nail dystrophy), gastrointestinal polyposis (hamartomatous and adenomatous polyps), markedly thickened gastric mucosa and folds, abdominal pain, weight loss, and marked foveolar gland hyperplasia; all was in favour of the CCS. On the other hand, there was no protein-losing enteropathy, diarrhea, hypoalbuminaemia, or skin pigmentation.

Lymphoma was excluded due to sparing of the muscularis propria. Furthermore, markedly thickened gastric mucosa and folds and the histopathological examination which revealed marked foveolar gland hyperplasia were consistent with MD. In addition, abdominal pain and weight loss are common presentation of MD, but the presence of colonic polyps, and antral and duodenal infiltration, and the absence of hypoproteinaemia decreased the possibility for MD.

The patient started a sequential therapy for *H. pylori* infection with complete eradication, followed by a proton pump inhibitor (40 mg once daily), prednisolone (30 mg/d), and mesalazine (500 mg QID) for 6 mo.

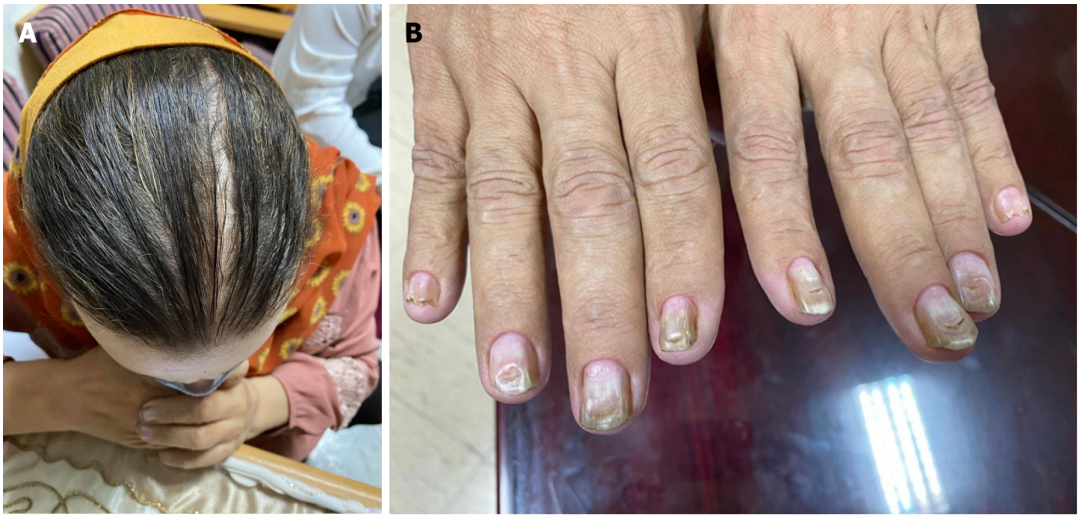

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Figure 1 Physical examination. A: Alopecia; B: Onychodystrophy.

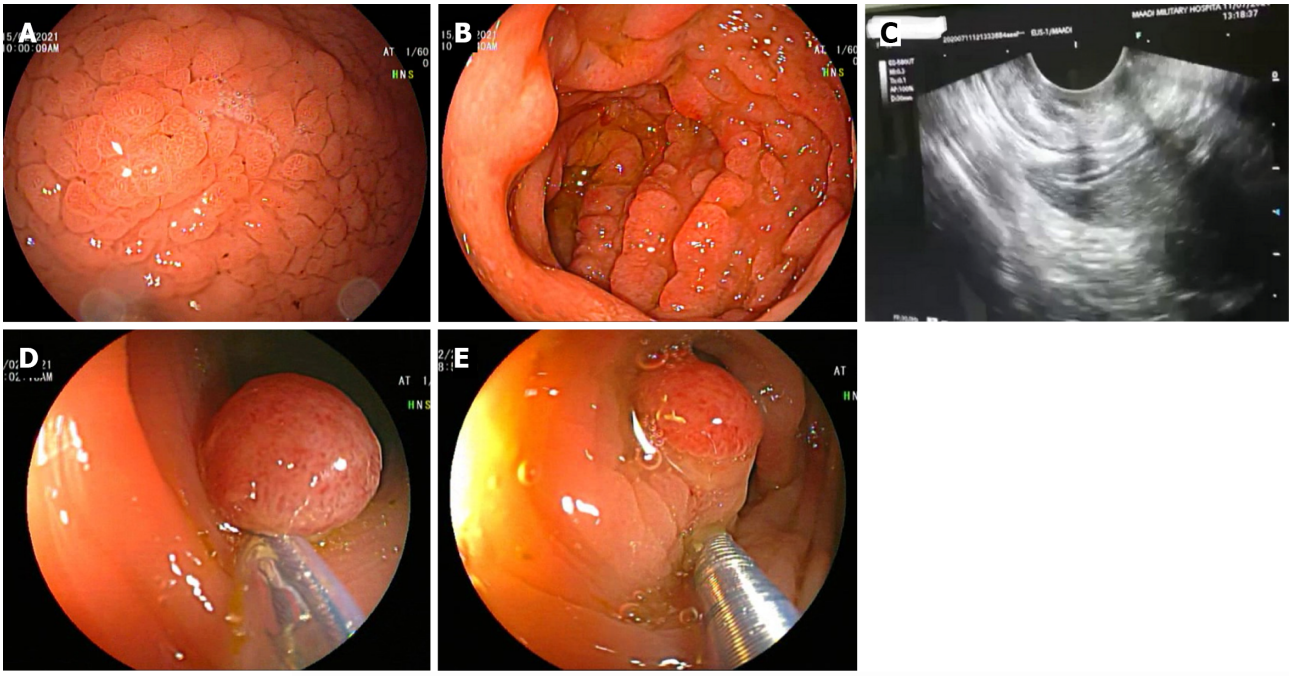

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Figure 2 Endoscopy. A and B: Upper endoscopy revealed a diffuse markedly thickened gastric mucosa with numerous polypoidal lesions; C: Endoscopic ultrasound revealed a significantly hypertrophic mucosa and muscularis mucosa, but sparing of the submucosa and the muscularis propria; D and E: Colonoscopy showed multiple variable-sized, sessile, and pedunculated polyps, which were removed by snare polypectomy.

Common complications of CCS include anemia, intussusception, rectal prolapse, and GI bleeding, as well as other less common ones such as recurrent severe acute pancreatitis, myelodysplastic syndrome, cecal intussusception, portal thrombosis, membranous glomerulonephritis, and osteoporotic fractures that may result from malabsorption of calcium or prolonged glucocorticoid therapy or both. The most serious complication is malignancy; however, the incidence of CCS-related cancer is estimated to be 5%-25%, especially gastric and colon cancer[6].

The follow-up endoscopies (OGD and colonoscopy) after 6 and 12 mo of treatment showed significant remission with a reduced number of gastric and colonic polyps and regression of hypertrophic gastric folds (Figure 4). Consequently, the patient's clinical condition was markedly improved, and the prednisolone dose was reduced gradually to 7.5 mg/d, but the mesalazine dose remained the same.

There is a tendency of malignant transformation or coexistence of gastrointestinal malignancies in patients with CCS. Therefore, endoscopic documentation of regression in CCS is important despite the

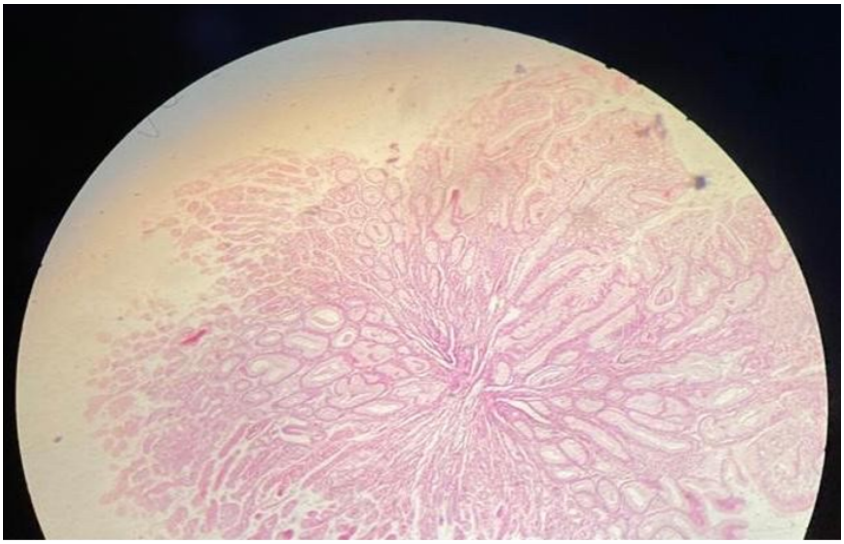

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Figure 3 Histopathological examination showed marked hyperplasia and cystic dilation of foveolar glands with inflammatory cell infiltration including eosinophils, chronic gastritis, and *Helicobacter pylori* infection with no atypia or malignancy.

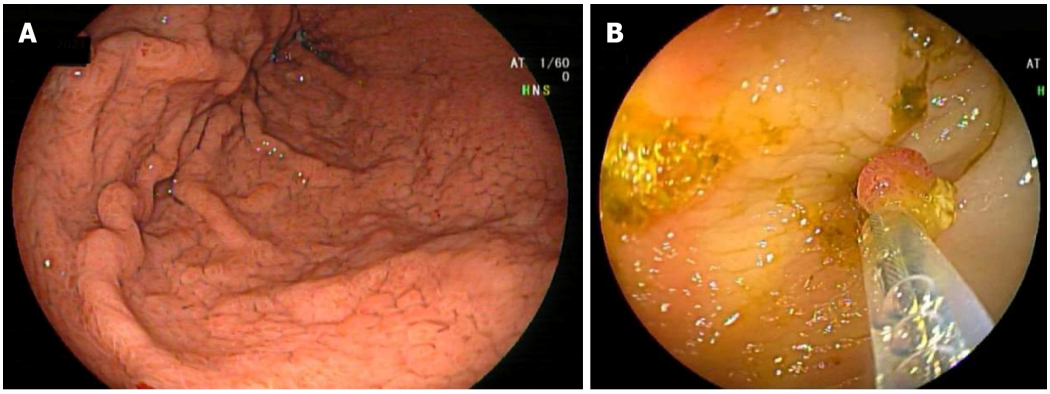

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Figure 4 Follow-up endoscopies after 6 mo and 12 mo of treatment showed significant remission with a reduced number of gastric and colonic polyps and regression of hypertrophic gastric folds. A: Upper endoscopy; B: Colonoscopy.

lower incidence of CCS-related cancer in remission patients. Therefore, the comprehensive endoscopic annual surveillance either *via* chromoendoscopy or directed biopsy from irregular polyps, to exclude pre-cancer lesions before development of invasive carcinoma is mandatory; however, there are still no recommended guidelines to be followed[7].

Nutritional support, electrolytes, and mineral and vitamin supplementation remain the cornerstone in treatment of CCS beside antibiotics and corticosteroids; however, the definitive treatment is still unknown[4,7].

Till now, there is still much that needs to know about this syndrome. In this context, the most important issue is to maintain treatment monitoring and provide appropriate measure to prevent relapse[8].

CONCLUSION

CCS is a form of uncommon, acquired polyposis with obscure aetiology. To date around 500 cases have been reported all over the world. Most of CCS cases were reported from Japan, and to our knowledge, our case is the first case reported from Egypt and North Africa. CCS is generally characterized by GI symptoms, such as diarrhea and skin changes (*e.g.*, alopecia, skin pigmentation, and onychodystrophy), while GI polyposis is the main endoscopic feature in CCS, which is commonly non-neoplastic and mainly include inflammatory, hyperplastic, hamartomatous, and/or adenomatous polyps. CCS has a malignant potential, and some cases may develop gastric and colorectal malignancies during the disease

course. Till now, there is no uniform standard treatment for CCS.

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FOOTNOTES

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CASE REPORT

Gastrointestinal histoplasmosis complicating pediatric Crohn disease: A case report and review of literature

C Quinn Miller, Omer A M Saeed, Katrina Collins

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Abstract

BACKGROUND

Infection with *Histoplasma capsulatum* (*H. capsulatum*) can lead to disseminated disease involving the gastrointestinal tract presenting as diffuse abdominal pain and diarrhea which may mimic inflammatory bowel disease (IBD).

CASE SUMMARY

We report a case of 12-year-old boy with presumptive diagnosis of Crohn disease (CD) that presented with several months of abdominal pain, weight loss and bloody diarrhea. Colonoscopy showed patchy moderate inflammation characterized by erythema and numerous pseudopolyps involving the terminal ileum, cecum, and ascending colon. Histologic sections from the colon biopsy revealed diffuse cellular infiltrate within the lamina propria with scattered histiocytic aggregates, and occasional non-necrotizing granulomas. Grocott-Gomori's Methenamine Silver staining confirmed the presence of numerous yeast forms suggestive of *Histoplasma* spp., further confirmed with positive urine *Histoplasma* antigen (6.58 ng/mL, range 0.2-20 ng/mL) and serum immunoglobulin G antibodies to *Histoplasma* (35.9 EU, range 10.0-80.0 EU). Intravenous amphotericin was administered then transitioned to oral itraconazole. Follow-up computed tomography imaging showed a left lower lung nodule and mesenteric lymphadenopathy consistent with disseminated histoplasmosis infection.

CONCLUSION

Gastrointestinal involvement with *H. capsulatum* with no accompanying respiratory symptoms is exceedingly rare and recognition is often delayed due to the overlapping clinical manifestations of IBD. This case illustrates the importance of excluding infectious etiologies in patients with "biopsy-proven" CD prior to initiating immunosuppressive therapies. Communication between clinicians and pathologists is crucial as blood cultures and antigen testing are key studies that should be performed in all suspected cases of histoplasmosis to avoid misdiagnosis and inappropriate treatment.

Key Words: Crohn disease; Disseminated histoplasmosis; Endoscopy; Colon; Inflammatory bowel disease; Immunosuppression; Case report

Core Tip: Impaired cell-mediated immunity is known to increase the risk for disseminated histoplasmosis and has been described in the setting of Crohn disease (CD) treated with immunosuppressant agents. Endoscopically, the appearance of histoplasmosis varies and includes features of inflammatory mucosal changes. Increasing awareness of this condition is critical to avoid misdiagnosis and inappropriate treatment, particularly in the setting of underlying CD. While no specific recommendations are available, immunosuppressive therapy may be safely initiated in some cases when there appears to be effective response to antifungal therapy and the patient can be monitored closely.

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INTRODUCTION

Histoplasmosis is an infection caused by inhalation of spores from the fungus *Histoplasma capsulatum* (*H. capsulatum*), found in soil enriched with bird and bat droppings and is endemic to the central and eastern states, prevalent in the Ohio and Mississippi River Valleys[1,2]. Clinical manifestations are typically self-limiting in immunocompetent children, whereas immunocompromised children are likely to present with more severe or disseminated disease and may be indistinguishable from malignancy or tuberculosis[3,4]. Single-organ histoplasmosis is rare, primarily affecting the lungs, occasionally lymph nodes, liver, bone marrow, skin and mucosal membranes[5-8]. While the literature contains many reports of disseminated histoplasmosis reminiscent of Crohn disease (CD) radiographically and endoscopically in immunocompromised patients, there are relatively few reports of symptomatic gastrointestinal histoplasmosis occurring in immunocompetent patients. The most commonly involved sites are the terminal ileum and the colon[9]. We report a case of an immunocompetent pediatric patient presenting with possible disseminated histoplasmosis after presumed initial diagnosis of CD. Early detection is critical to avoid treatment with immunosuppressive therapy and potential complications.

CASE PRESENTATION

Chief complaints

The patient is a 12-year-old boy who presented with several months of abdominal pain, weight loss, and bloody diarrhea.

History of present illness

The patient experienced abdominal pain, weight loss, and bloody diarrhea and was referred for upper and lower GI endoscopy with biopsy.

History of past illness

His medical history was remarkable for several mild and self-limiting respiratory illnesses with non-productive cough. The most recent episode occurred fourteen months prior to his current presentation.

Personal and family history

No notable personal or family medical history.

Physical examination

Unremarkable physical examination.

Laboratory examinations

Esophagogastroduodenoscopy was performed and revealed focally ulcerated gastric mucosa and several inflammatory polyps arising within the second and third portions of the duodenum.

Colonoscopy revealed patchy moderate inflammation characterized by erythema and numerous pseudopolyps involving the terminal ileum, cecum, and ascending colon (Figure 1). An erythematous region containing shallow ulcers was identified at the hepatic flexure. Multiple biopsies were taken from throughout the colon. A presumptive diagnosis of CD was made, methylprednisolone (40 mg/kg/d, IV) was administered and the patient was then discharged on oral prednisone (40 mg, QD) and oral mesalamine (1000 mg, TID).

Histologic examination of an H&E-stained colonic biopsy revealed a diffuse cellular infiltrate within the lamina propria with scattered histiocytic aggregates and occasional non-necrotizing granulomas (Figure 2A-C). Grocott-Gomori's methenamine silver (GMS) and Periodic acid-Schiff stains confirmed the presence of numerous yeast forms morphologically suggestive of *H. capsulatum* (Figure 2D and E), further confirmed with positive urine *Histoplasma* antigen (6.58 ng/mL, positive range 0.2-20 ng/mL) and serum immunoglobulin G (IgG) antibodies to *Histoplasma* (35.9 EU, positive ≥ 10.0 EU).

Given the unusual nature of the histoplasmosis infection, an immunological workup was initiated and revealed profound hypogammaglobulinemia: Serum IgG 94 mg/dL (range 638-1453), IgM 9 mg/dL (range 56-242), and IgA 40 mg/dL (range 45-285) as well as CD8 lymphopenia (253/mm^3, range 331-1445). Genetic testing was ordered for inborn error of immunity using Invitae Primary Immunodeficiency Panel and one pathogenic variant was identified in CD40LG c.43del (pThr15Leufs*7), associated with X-linked hyper-IgM syndrome (XHIGM) and two likely pathogenic variants in TNFRSF13B c.310T>C (p.Cys104RG) (homozygous), associated with recessive common variable immunodeficiency (CVID).

Imaging examinations

Computed tomography (CT) of the chest, abdomen, and pelvis demonstrated a calcified left lower lobe lung nodule with associated hilar lymphadenopathy, diffuse colitis with wall thickening of the distal small bowel through the cecum, abdominal lymphadenopathy, and abnormal-appearing adrenal glands, likely related to disseminated histoplasmosis infection.

FINAL DIAGNOSIS

Combined with the patient's medical history, the final diagnosis was isolated gastrointestinal histoplasmosis complicating newly diagnosed, presumed CD.

TREATMENT

An induction regimen of liposomal amphotericin was administered (3 mg/kg/d, IV) followed by 1 year of oral itraconazole (200 mg, BID) and treatment with oral mesalamine (1000 mg, TID) to maintain endoscopic remission with plans for endoscopy and colonoscopy in the future after trailing off medication at 6 mo.

OUTCOME AND FOLLOW-UP

Ongoing follow-up is planned for diagnostic evaluation of CD and the treatment plan includes maintaining clinical improvement and *Histoplasma* antigen clearance. Decisions on whether to initiate treatment for CD are pending as duration of antifungal therapy and safety of immunosuppressive therapy are to be determined. To date, our patient has completed 5 mo of a 12-mo course of antifungal therapy and is maintained on mesalamine until follow-up endoscopy and colonoscopy. The patient's symptoms have largely resolved and remain stable after 5 mo of follow-up.

DISCUSSION

Gastrointestinal involvement commonly occurs as part of disseminated histoplasmosis; however isolated colonic involvement with lack of respiratory symptoms is rare[10]. Histoplasmosis can occur at any age. Nonspecific clinical manifestations of gastrointestinal involvement such as abdominal pain, fever, weight loss, and diarrhea are variably present and may only be mild[6,10,11]. Immunocompromised patients are at increased risk of developing disseminated disease and may experience complications such as bleeding or intestinal obstruction more readily than immunocompetent individuals. A high index of suspicion is required for diagnosing histoplasmosis and the gold standard for diagnosis includes isolation of the fungus in blood culture and antigen testing in suspected cases, as utilizing both serum and urine consistently provides the highest sensitivity for detection. Testing for

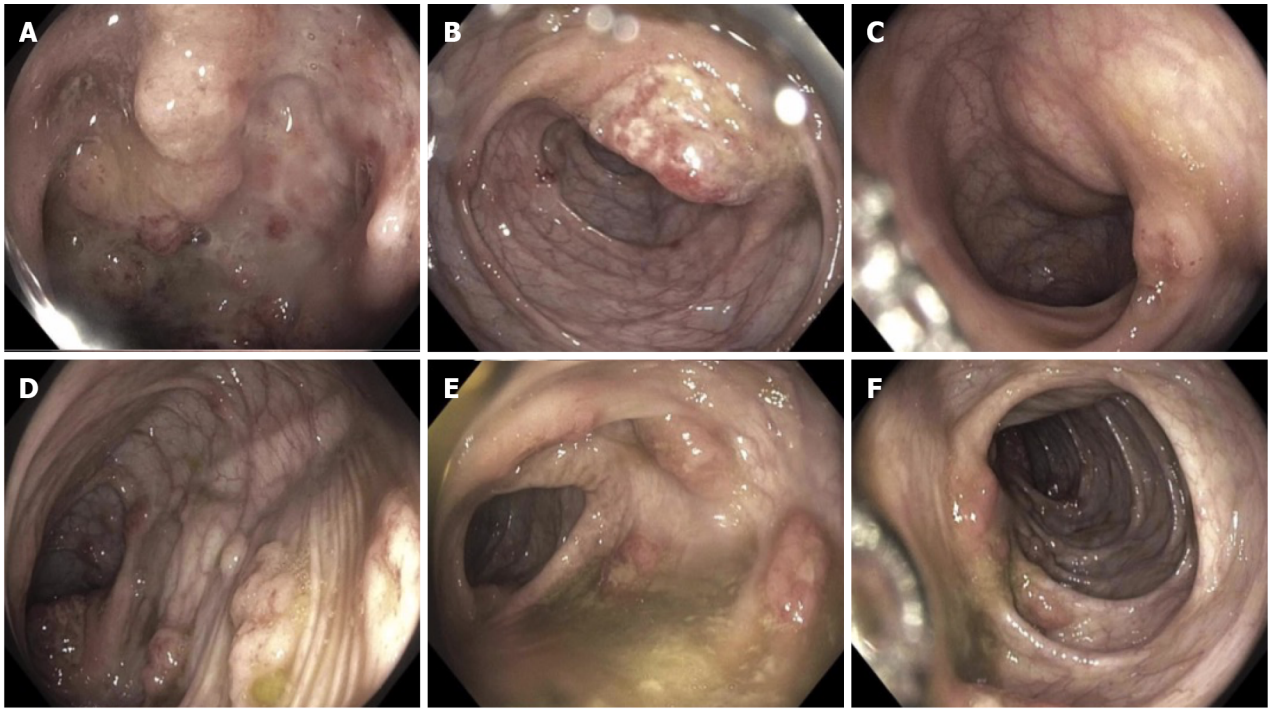

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Figure 1 Colonoscopy findings. Diffuse and severe inflammation characterized by mucosal edema, erythema, friability, pseudopolyps, and serpentine ulcerations. A: Terminal ileum; B: Ileocecal valve; C: Transverse colon; D and E: Descending colon; F: Ascending colon.

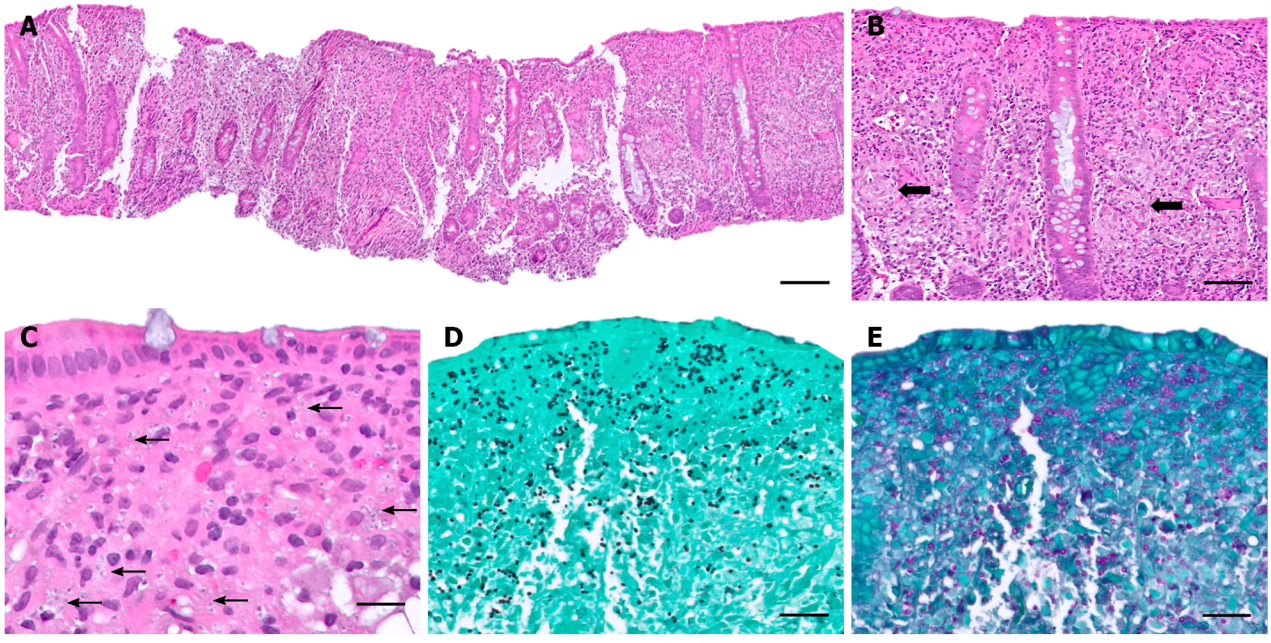

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Figure 2 Histologic findings. A: Colon biopsy revealed diffuse cellular infiltrate within the lamina propria (hematoxlyin and eosin, × 2, scale bar 1 mm); B: Scattered poorly formed granulomas (arrows) (hematoxlyin and eosin, × 20, scale bar 100 μm); C: Intracellular microorganisms (arrows) (hematoxlyin and eosin, × 40, scale bar 50 μm); Numerous yeast forms suggestive of *Histoplasma* spp. confirmed by special stains; D: Grocott-Gomori's Methenamine Silver stain (× 20, scale bar 100 μm); E: Periodic acid Schiff stain (× 20, scale bar 100 μm).

anti-*Histoplasma* antibodies further increases the sensitivity for diagnosis[12].

The terminal ileum is most commonly involved, presumably because of the lymphoid-rich tissue in this area, but can be found throughout the gastrointestinal tract[9]. The pathologic findings of gastrointestinal histoplasmosis include mucosal ulceration, polypoid lesions, and obstructing masses[6,11,13]. Histologically, tissue shows diffuse expansion of lamina propria and submucosa by macrophages containing intracellular yeast forms[6,10]. As in our case, due to similarities in presentation, pattern of

Table 1 Reports of histoplasmosis mimicking inflammatory bowel disease in pediatric immunocompetent patients: Cases published between 1970–present (including current case)

Ref.	No. of cases	Age/Sex	Clinical presentation	Initial concern	Immune status	Laboratory investigations
Soper *et al* [23], 1970	2	15/M	Periumbilical pain with radiation to back; prior exposure to *Coccidioides* and *Histoplasma*	Presumed CD	Immunocompetent	*Histoplasma* antibody titers 1:1024
		13/M	Abd pain, bilious vomiting, weight loss, fever; prior exposure to *Histoplasma*	Presumed CD	Immunocompetent	Not performed
Alberti-Flor and Granda [18], 1986	1	16/M	Abd pain, diarrhea, weakness, fever; history of Job syndrome	Presumed CD	Hyper-IgE syndrome	Complement fixation 1:64; yeast antigen 1:8; preciptin (H/M bands), GMS+ yeast forms (resection specimen)
Steiner *et al* [19], 2009	1	14/F	Fatigue, abd pain, fever, weight loss	Presumed CD	Hyper-IgE syndrome	Urine *Histoplasma* antigen (8.34 ng/mL), *Histoplasma* complement fixation titers 1:32 (mycelial phase) 1:64 (yeast phase), preciptin (H/M bands), Yeast forms (terminal ileum, ileocecal valve)
Agarwal *et al* [20], 2015	1	7/F	Intermittent fever and chills, weight loss	Presumed CD	Immunocompetent	Yeast forms (peripheral blood), GMS/PAS+ yeast forms (bone marrow)
Kweyamba *et al*[21], 2016	1	4/M	Intermittent vague abd pain, anorexia, occasional vomiting and nausea; obstructing mesenteric chylous cyst	Intestinal obstruction	Immunocompetent	PAS+ yeast forms (cyst lining)
Acharyya *et al* [22], 2021	1	8/M	Colicky abd pain, weight loss, constipation, subsequent ileal stricture	Presumed intestinal tuberculsosis, unresponsive to antitubercular medication × 9 mo	Immunocompetent	GMS+ yeast forms (ileum, mesenteric nodes)
Current case, 2022	1	12/M	Abdominal pain × several months, weight loss, bloody diarrhea	Presumed CD	Immunocompetent	GMS+ yeast forms (colon)

6-MP: 6-mercaptopurine; abd: Abdominal; CD: Crohn disease; GI: Gastrointestinal; IBD: Inflammatory bowel disease; NR: Not reported; UC: Ulcerative colitis.

involvement and associated granulomatous inflammation, gastrointestinal histoplasmosis can mimic CD[6,14-17].

To our knowledge, only 7 cases of isolated gastrointestinal histoplasmosis occurring in the pediatric age group (younger than 18 years of age) have been previously reported, mostly from individual case reports (Table 1)[18-22] and one small case series[23]. Ages ranged from 4 to 16 years with a median age of 13 years. Of the previously described cases, the male/female ratio was 5:2. Our patient presented at a slightly younger age than the median (12 years *vs* 13 years). The most common presenting symptoms included abdominal pain and weight loss, with diarrhea, anorexia, and fever appearing occasionally. Pulmonary symptoms at presentation or during the disease course were not reported in any case. Five patients were presumed immunocompetent[20-22], while two patients were known to have immunocompromising conditions (hyper-IgE syndrome) prior to their presentation[18,19]. One patient with hyper-IgE syndrome was effectively treated seven months prior for cough and fever of unknown origin [19]. As in our case, five patients were given a presumptive diagnosis of CD based on clinical presentation and endoscopic findings[20-23]. A broad range of diagnostic laboratory tests were performed including immunological tests for antigen and/or antibody detection. Microscopic examination revealed the presence of yeast forms (by routine hematoxylin and eosin staining and/or special staining methods) in all cases.

In our present case, the patient presented with gastrointestinal symptoms alone and endoscopic findings suggestive for CD and was started on corticosteroids and subsequently mesalamine. An interesting feature of our case is that while the gastrointestinal tract was the only site of symptomatic disease, it is unlikely to be the primary focus of infection. It is more likely that after inhalation of the fungus, dissemination by the bloodstream occurred before an immune response was mounted with some unidentifiable factor favoring persistence in the gastrointestinal tract exclusively. After additional workup, the patient was identified as more susceptible to histoplasmosis because of the dysregulation of cell-mediated immunity associated with his XHIGM and CVID, as suggested by his immunological

Table 2 Infectious mimics of inflammatory bowel disease[1]

Infectious etiology	Gastrointestinal site	Routine stain	Ancillary stain(s)
Bacterial			
E. coli, O157-H7[24]	Colon	H&E stain	Gram stain
Shigella spp.[25]	Colon		
Salmonella spp.[26]	Colon, terminal ileum		
Campylobacter spp.[27]	Colon, terminal ileum		
Yersinia enterocolitica[28]	Colon, terminal ileum		
Clostridiodes difficile[29]	Colon		
Nesisseria gonorrhoeae[30]	Colorectal		
Treponema pallidum[31]	Colorectal		
Chlamydia trachomatis[32]	Colorectal		
Aeromonas spp.[33]	Colon		
Mycobacterial tuberculosis[34]	Gastrointestinal tract, mostly terminal ileum		Gram stain Acid-fast stain (Ziehl-Neelsen or Kinyoun)
Fungal			
Cryptococcus spp.[35]	Terminal ileum	H&E stain	GMS stain
Histoplasma capsulatum[36]	Terminal ileum		PAS stain
Coccidioides spp.[37]	Colon		
Paracoccidioides spp.[38]	Colorectal		
Viral			
Cytomegalovirus[39]	Jejunoileal	H&E stain	CMV immunostain
Herpes simplex virus[40]	Colorectal		HSV I/II immunostain
Parasite			
Entamoeba histolytica[41]	Colon	H&E stain	Giemsa stain
Enterobius vermicularis[42]	Colorectal		Serology
Taenia saginata[43]	Ileum		Stool examination
Strongyloides stercoralis[44]	Colon		
Anisakis spp.[45]	Ileum		
Hookworm (*Ancylostoma duodenale, Necator americanus*)[46]	Jejunoileal		

[1]Adapted from Shojaei *et al*[47].
CMV: Cytomegalovirus; GMS: Grocott-Gomori's Methenamine Silver; H&E: Hematoxylin and eosin; HSV: Herpes simplex virus; PAS: Periodic acid-Schiff.

testing results. Distinction of these entities is vital as the optimal treatment for one disease could lead to exacerbation of the other. A list of infectious diseases that should be excluded in patients diagnosed as inflammatory bowel disease (IBD) is provided in Table 2.

CONCLUSION

Gastrointestinal involvement with *H. capsulatum* in the absence of pulmonary manifestations is exceedingly rare and may lead to delay in recognition due to overlapping symptoms with IBD. This case highlights the importance of excluding infectious etiologies in patients with "biopsy-proven" CD prior to initiating immunosuppressive therapies, especially in the setting of recent travel or exposure in an endemic area. Communication between clinicians and pathologists is crucial as tests for *Histoplasma*

antigen in urine or serum should be performed once histoplasmosis is suspected.

FOOTNOTES

Author contributions: Miller CQ served as the primary author; Miller CQ and Collins K are responsible for this literature review; Miller CQ, Saeed OAM, and Collins K were responsible in the construction of the manuscript; Collins K served as the senior author, provided invaluable educational input and managed the edits of the manuscript, and guided the primary author through the submission process; All authors read, revised, and gave approval of the manuscript.

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OPINION REVIEW

Current approaches and questions yet to be resolved for the prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis

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Abstract

Prophylaxis is important for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP), which is the most common and serious complication of ERCP. Although the current guidelines include independent patient- and procedure-related risk factors for PEP and available PEP prophylactic measures, the synergistic effect of these risk factors on PEP should also be considered, given that patients often harbor multiple risk factors. Furthermore, a combination of prophylactic measures is often selected in clinical practice. However, established methods estimating the synergistic effect of independent risk factors on PEP incidence are lacking, and evidence on the impact of combining prophylactic measures on PEP should be discussed. Selection of appropriate candidate patients for ERCP is also important to reduce the incidence of PEP associated with unnecessary ERCP. ERCP indications in patients with asymptomatic common bile duct stones (CBDSs) and in those with suspected CBDSs with no imaging-based evidence of stones are controversial. Further studies are warranted to predict the synergistic effect of independent risk factors on PEP, determine the best prophylactic PEP measures, and identify appropriate candidates for ERCP in patients with asymptomatic CBDSs and those with suspected CBDSs.

Key Words: Endoscopic retrograde cholangiopancreatography; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Prophylaxis; Guidelines

Core Tip: To date, there are no established methods to estimate the synergistic effect of the independent risk factors on post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP), and evidence of the efficacy of the combination of prophylactic measures for PEP should be discussed. Furthermore, ERCP indications in patients with asymptomatic common bile duct stones (CBDSs) and patients with suspected CBDS without evidence of stones by imaging are controversial. Further studies are warranted to estimate the synergistic effect of independent risk factors on PEP and to determine the best prophylactic measures as well as the appropriate candidates for ERCP among patients with asymptomatic CBDS and those with suspected CBDS.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an essential therapeutic procedure for patients with biliopancreatic disorders. However, it is associated with high risks of procedure-related complications. Post-ERCP pancreatitis (PEP) is the most frequent complication, with an approximate rate of 3%-10%[1,2]. A meta-analysis of 108 randomized controlled trials revealed that the incidence of PEP was high at 14.7% [95% confidence interval (CI) 11.8%-17.7%] in high-risk patients, with one or more patient- and/or procedure-related risk factors for PEP[2]. Although most PEP cases are mild or moderate, severe PEP, which is potentially lethal, occurs in approximately 10% of the cases[1]. Therefore, it is important to reduce the incidence of PEP.

Recent guidelines published by the European Society of Gastrointestinal Endoscopy (ESGE) and the American Society for Gastrointestinal Endoscopy (ASGE) recommend prophylactic methods for reducing the incidence of PEP[3,4]. These guidelines encompass patient- and procedure-related risk factors associated with PEP and strategies for reducing the incidence of PEP, including patient selection, pharmacologic prophylaxis, and ERCP technique modifications. This opinion review discusses the current approaches used in PEP prevention and the questions yet to be resolved for the prophylaxis of PEP to further reduce the incidence of PEP.

RISK FACTORS FOR PEP

Table 1 summarizes the independent risk factors for PEP included in the ESGE and ASGE guidelines for ERCP-related adverse events[3,4]. Specifically, the ESGE guideline categorizes independent PEP risk factors into definitive and likely risk factors, and patients with at least one definitive or two likely patient- or procedure-related risk factors are defined as those at a high risk for PEP[3].

Patients often harbor multiple risk factors for PEP; therefore, the potential synergistic effect of independent risk factors for PEP should be considered. A prospective multicenter study revealed the escalation of PEP risk in patients with multiple risk factors for PEP. The odds ratios in female gender alone, female gender plus normal serum bilirubin, and female gender plus normal serum bilirubin plus difficult cannulation were 2.5, 4.8 and 16.2, respectively[5]. Although scoring systems may be useful for estimating this synergistic effect[6-10], no established scoring system exists due to the limited number of studies. Furthermore, estimating the risk for PEP before ERCP is important for advanced counseling of patients on the specific risk for PEP. A recent study suggesting a disease-based PEP risk stratification approach for choledocholithiasis reported that the incidence rates of PEP were 13.7%, 7.3%, and 1.8% in patients with asymptomatic common bile duct stones (CBDSs), obstructive jaundice without cholangitis, and acute cholangitis, respectively[11]. Disease-based risk stratification may be a useful method for easily estimating the average risk for PEP before ERCP in patients with biliary and pancreatic diseases as the synergistic effect of the independent risk factors for PEP may differ among the wide range of diseases requiring ERCP. Furthermore, a study demonstrated that a large pancreatic volume was associated with high risk and increased severity of PEP[12]. Pancreatic volume based on pre-ERCP images may also be useful for predicting the risk for PEP prior to ERCP.

In summary, although several independent risk factors for PEP have been identified[3,4,13], further studies are warranted to establish the methods for estimating the synergistic effect of independent risk factors for PEP. If possible, advanced prediction of PEP before ERCP is desirable to properly counsel patients on the specific risk for PEP and to perform aggressive prophylaxis prior to ERCP based on the

Table 1 Risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis in the European Society of Gastrointestinal Endoscopy and American Society for Gastrointestinal Endoscopy guidelines

ESGE guideline	ASGE guideline
Patient-related definitive risk factors	**Patient-related risk factors**
Suspected sphincter of Oddi dysfunction	Suspected sphincter of Oddi dysfunction
Female sex	Female sex
Previous pancreatitis	Previous recurrent pancreatitis
Previous post-ERCP pancreatitis	Previous post-ERCP pancreatitis
Procedure-related definitive risk factors	Younger age
Difficult cannulation	Absence of chronic pancreatitis
More than one pancreatic guidewire passage	Normal serum bilirubin
Pancreatic injection	**Procedure-related risk factors**
Patient-related likely risk factors	Difficult cannulation (> 10 min)
Younger age	Repeated pancreatic guidewire cannulation
Nondilated extrahepatic bile duct	Pancreatic injection
Absence of chronic pancreatitis	Endoscopic papillary large-balloon dilation of a native papilla
Normal serum bilirubin	
End-stage renal failure	
Procedure-related likely risk factors	
Precut sphincterotomy	
Pancreatic sphincterotomy	
Papillary balloon dilation	
Unsuccessful clearance of bile duct stones	
Intraductal ultrasound	

ASGE: American Society for Gastrointestinal Endoscopy; ERCP: Endoscopic retrograde cholangiopancreatography; ESGE: European Society of Gastrointestinal Endoscopy.

specific PEP risk of the patient.

PATIENT SELECTION

Selection of appropriate candidates for ERCP is important to reduce the incidence of PEP associated with unnecessary ERCP. Patients with biliary and pancreatic diseases requiring drainage, such as malignant biliary and pancreatic strictures and symptomatic choledocholithiasis with imaging-based evidence of CBDSs, are strong candidates for ERCP. However, determining ERCP candidates may be difficult in patients with asymptomatic CBDSs and suspected choledocholithiasis with no imaging-based evidence of stones.

The ASGE and ESGE guidelines for the evaluation and management of choledocholithiasis recommend strategies for selecting ERCP candidates in patients with suspected CBDSs based on stratification into low-, intermediate-, and high-PEP-risk groups[14,15]. The criteria and treatment strategy for each risk group are presented in Table 2. In these guidelines, proceeding with ERCP is recommended in high-risk patients regardless of the imaging-based evidence of CBDSs. However, the high-diagnostic ability of imaging modalities, such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS), has been recently described. Two meta-analyses reported that the sensitivity and specificity of EUS were 95%-97% and 87%-93%, and that the sensitivity and specificity of MRCP were 90%-97% and 92%-96%, respectively[16,17]. The rate of detecting even small CBDSs was high with EUS[16]. However, a systematic review and meta-analysis revealed that the mean sensitivity and specificity for the diagnosis of CBDSs were 23% (range, 18%-32%) and 89% (range, 70%-100%), respectively, when acute cholangitis was used to predict the presence of CBDSs in patients with suspected CBDSs[18]. Furthermore, one study reported that the sensitivity and specificity for the

Table 2 Recommended strategies for suspected common bile duct stones in patients with symptomatic cholelithiasis based on the ESGE and ASGE guidelines

ESGE guideline			ASGE guideline	
Likelihood	Predictors	Recommended strategy	Predictors	Recommended strategy
Low	Normal liver function tests and no CBD dilation at US	Proceed to cholecystectomy	No predictors	Cholecystectomy with/without laparoscopic cholangiography (IOC) or intraoperative US
Intermediate	Abnormal liver function tests and/or dilated CBD on US	Perform EUS/MRCP	Abnormal liver function tests or age > 55 years or dilated CBD on US/cross-sectional imaging	Perform EUS/MRCP, laparoscopic IOC, or intraoperative US
High	CBDSs identified at US or features of cholangitis	Proceed to ERCP	CBDSs identified at US/cross-sectional imaging or features of cholangitis or dilated CBD with total bilirubin > 4 mg/dL on US/cross-sectional imaging	Proceed to ERCP

ASGE: American Society for Gastrointestinal Endoscopy; CBD: Common bile duct; CBDSs: Common bile duct stones; ERCP: Endoscopic retrograde cholangiopancreatography; ESGE: European Society of Gastrointestinal Endoscopy; EUS: Endoscopic ultrasonography; MRCP: Magnetic resonance cholangiopancreatography; US: Ultrasonography.

diagnosis of CBDSs were 19% and 96%, respectively, using the high-risk criteria of a total bilirubin level of above 4 mg/dL plus the presence of a dilated common bile duct (CBD) (> 6 mm in patients without cholecystectomy and > 8 mm in those with prior cholecystectomy)[19]. Therefore, high-risk criteria for diagnosis of CBDSs based on the clinical diagnosis, such as cholangitis features and dilated CBD with a total bilirubin level > 4 mg/dL without evidence of stones remains controversial. Patients with suspected CBDSs who exhibit imaging-based evidence of CBDSs are strong candidates for ERCP. However, it remains questionable whether ERCP is indicated in high-risk patients with no imaging-based evidence of stones, except for those with severe cholangitis requiring emergent biliary drainage.

Several studies have demonstrated that the incidence of PEP is significantly higher in patients with asymptomatic CBDSs, defined as the absence of abdominal symptoms and abnormal liver function tests, than in those with symptomatic CBDSs (12.5%-20.8% *vs* 3.7%-6.9%)[20-23], although only one study reported that the risk for PEP following ERCP performed by experienced endoscopists was comparable between patients with asymptomatic and symptomatic CBDSs[24]. Due to the absence of cholestasis, patients with asymptomatic CBDSs have normal total bilirubin levels and nondilated CBD, and can confound the assessment of patient-related risk factors for PEP[21]. Furthermore, floppy major duodenal papilla due to low bile duct pressure often results in difficult biliary cannulation in asymptomatic patients[21]. Therefore, the risk of PEP might be higher in patients with asymptomatic CBDSs, who are susceptible to the synergistic effect of the independent risk factors for PEP, than in those with symptomatic CBDSs.

Studies investigating the natural history of asymptomatic CBDSs have demonstrated that the cumulative incidence rate of biliary complications ranges from 0% to 29% during a median follow-up period of 30 days to 4.8 years[25-29]. Although available guidelines recommend endoscopic stone removal even in asymptomatic patients[14,15,30,31], prospective studies comparing the long-term outcomes between endoscopic treatment and the wait-and-see strategy for patients with asymptomatic CBDSs are warranted to determine whether routine endoscopic stone removal of asymptomatic CBDS is justified or not.

A recent study reported that the risk for PEP was lower in ERCP for choledocholithiasis with acute cholangitis than in ERCP for choledocholithiasis without acute cholangitis[32]. Although ESGE guideline for the endoscopic management of CBDS recommends elective ERCP for mild cholangitis, performing ERCP before improving cholangitis may be better in the view point of reducing the risk of PEP.

MODIFICATIONS IN ERCP TECHNIQUE AND PHARMACOLOGICAL PROPHYLAXIS TO REDUCE THE INCIDENCE AND SEVERITY OF PEP

PEP prophylaxis during ERCP

Recommendations for post-ERCP pancreatitis prophylaxis in ASGE and ESGE guidelines are presented in Table 3.

Table 3 Recommendations for post-endoscopic retrograde cholangiopancreatography pancreatitis prophylaxis in American Society for Gastrointestinal Endoscopy and European Society of Gastrointestinal Endoscopy guidelines

ASGE guideline	ESGE guideline
PEP prophylaxis during ERCP	**PEP prophylaxis during ERCP**
Pancreatic duct stenting in high-risk patients (high quality of evidence)	Pancreatic duct stenting in high-risk patients (strong recommendation, moderate quality of evidence)
Early precut sphincterotomy for difficult cannulation (moderate quality of evidence)	
Pharmacologic methods for PEP prophylaxis	**Pharmacologic methods for PEP prophylaxis**
Rectal NSAIDs in high-risk patients without contraindication (moderate quality of evidence)	Routine rectal NSAIDs of 100 mg of diclofenac or indomethacin immediately before in all patients without contraindication (strong recommendation, moderate quality of evidence)
Rectal indomethacin in average-risk patients without contraindication (moderate quality of evidence)	Hydration with lactated ringers in patients with contraindication to NSAIDs without at risk of fluid overload and without prophylactic pancreatic stenting (strong recommendation, moderate quality of evidence)
Hydration with lactated ringers (very-low quality of evidence)	Not suggested for the routine combination of rectal NSAIDs with other prophylactic measures (weak recommendation, low quality of evidence)
	Not recommended for protease inhibitors and epinephrine onto the papilla (strong recommendation, moderate quality of evidence)
	Somatostatin and octoreotide (no recommendation)

ERCP: Endoscopic retrograde cholangiopancreatography; ASGE: American Society for Gastrointestinal Endoscopy; ESGE: European Society of Gastrointestinal Endoscopy; PEP: Post-endoscopic retrograde cholangiopancreatography pancreatitis; NSAIDs: Nonsteroidal anti-inflammatory drugs.

Prophylactic pancreatic stent placement is a well-known effective method for PEP prophylaxis. Several meta-analyses have indicated that prophylactic pancreatic stent is associated with the decreased overall incidence of PEP (odds ratio, 0.22-0.39) and decreased incidence of severe PEP[33-38]. However, evidence for the benefit of salvage pancreatic stenting in patients with PEP is lacking. Two studies demonstrated that salvage pancreatic stenting might be useful for the rapid resolution of PEP and halting progression to severe PEP[39,40]. The ESGE guidelines recommend against the use of salvage pancreatic stenting in patients with PEP due to the limited evidence; however, this approach has been recommended in select patients, such as those with PEP accompanied by severe abdominal pain and those with more than 10-fold increase in serum amylase levels[3].

Pancreatic injection is a procedure-related definitive risk factor for PEP[3]. The use of low-osmolality contrast media, which might be less harmful for the epithelium of pancreatic duct compared with high-osmolality contrast media[41], may be a possible approach to prevent PEP. However, studies evaluating the efficacy of low-osmolality contrast medium for PEP prevention have reported contradictory findings [41-44].

Difficult biliary cannulation is another definitive risk factor for PEP[3,4]. Although the definition of difficult cannulation varies among the previous studies, the ESGE guidelines for papillary cannulation and sphincterotomy technique in ERCP define difficult cannulation as cases fulfilling one or more of several criteria, such as more than five contacts with the major duodenal papilla during the cannulation attempt, cannulation attempt lasting more than 5 min after the visualization of the papilla, and more than one unintended cannulation or opacification of the pancreatic duct[45]. In cases with difficult biliary cannulation, pancreatic guidewire-assisted cannulation and precut sphincterotomy are used as well-known rescue techniques. Several studies have demonstrated the safety and efficacy of early precut sphincterotomy in reducing the risk of PEP. A recent systematic review and network meta-analysis revealed that early precut sphincterotomy was associated with increased successful biliary cannulation and reduced incidence of PEP compared with the standard cannulation technique and pancreatic guidewire-assisted cannulation[46]. Furthermore, a retrospective study demonstrated that the second ERCP after the failure of initial biliary cannulation following precut sphincterotomy should be performed at least 4 days after the first ERCP[47]. However, a few studies investigated the efficacy and safety of the early use of double-guidewire technique. A randomized controlled trial revealed that the early use of double-guidewire technique increased the rate of successful biliary cannulation and that the incidence of PEP was similar between the double-guidewire technique and the repeated use of single-guidewire technique[48]. Another randomized controlled trial demonstrated that the early use of double-guidewire technique did not facilitate successful biliary cannulation and did not reduce the incidence of PEP[49]. Further studies are warranted to evaluate the efficacy and safety of early use of pancreatic guidewire-assisted cannulation. Furthermore, the optimal timing for the rescue cannulation technique is unclear, although one study suggested that attempting biliary cannulation for 5 min might be a valid cutoff for the implementation of the rescue technique[50].

Pharmacologic methods for PEP prophylaxis

Rectal nonsteroidal anti-inflammatory drugs (NSAIDs) are consistently recommended as pharmacologic prophylaxis for PEP in the current guidelines[3,4]. Rectal diclofenac and indomethacin are considered to have a similar beneficial effect for the prophylaxis of PEP, and the rectal NSAID dose of 100 mg is recommended in the ASGE and ESGE guidelines[3,4]. However, the rectal NSAID dose of 100 mg may be too high for elderly patients or those with low body weight, especially among Asian populations. A randomized controlled trial revealed that the incidence of PEP was significantly lower in patients who were administrated 25-50-mg rectal NSAIDs than in those who were not administered rectal NSAIDs [3.9% (2/51) *vs* 18.9% (10/53)][51]. However, several retrospective and prospective studies demonstrated that low-dose rectal NSAIDs were not useful for reducing the risk for PEP[52-54]. Further studies are warranted to determine the optimal rectal NSAID dose in elderly patients and in those with low body weight. Studies investigating the combination of rectal NSAIDs with other prophylactic approaches for PEP found no difference in the PEP incidence between rectal NSAIDs alone and rectal NSAIDs in combination with prophylactic pancreatic stenting[55-57]. However, a recent study demonstrated that the combined approach of rectal NSIADs and prophylactic pancreatic stenting was useful for preventing PEP in patients undergoing ERCP using the double-guidewire technique[58].

Aggressive hydration is recognized as a useful method for PEP prophylaxis[3]. Recent meta-analyses revealed that aggressive hydration with the lactated Ringer's solution of 35-45 mL/kg administrated during 8-10 h contributed to reduce the incidence of PEP with odds ratios of 0.29–0.47[59-61]. Furthermore, aggressive hydration was associated with the decreased moderate to severe PEP with the odds ratio of 0.16[59], and there were no differences in fluid overload-related complications[60,61]. While several studies reported that rectal NSAIDs plus hydration was an effective combination for the prevention of PEP[37,62-65], others reported no benefit with this approach[66,67]. A recent network meta-analysis of 24 randomized controlled trials demonstrated that a combination of rectal indomethacin and aggressive hydration is the best conservative approach for prophylaxis of PEP with preventive efficacy 70%-99% higher than that of single prophylaxis[64]. In recent years, with the increasing implementation of prophylactic measures for PEP, the combination of various approaches is often selected in clinical practice[68]. Further studies are warranted to solve the dilemma of combining specific approaches for PEP prophylaxis.

CONCLUSION

Estimation of the PEP risk based on patient- and procedure-related risk factors, patient selection for ERCP, and technical and pharmacological prophylaxis for PEP are important aspects to be considered to reduce the incidence of PEP following ERCP. Although several independent patient- and procedure-related risk factors for PEP have been identified, methods for estimating the synergistic effect of these risk factors on PEP incidence should be established in future studies. Regarding patient selection, whether routine ERCP in cases of asymptomatic CBDSs and highly suspected CBDSs without imaging-based evidence of stones is warranted should be discussed. Furthermore, although independent prophylactic measures such as rectal NSAIDs and prophylactic pancreatic stenting have been implemented, further studies are warranted to determine the best prophylactic measures for PEP, including the combination of independent prophylactic measures.

FOOTNOTES

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MINIREVIEWS

Optimal traction direction in traction-assisted gastric endoscopic submucosal dissection

Mitsuru Nagata

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Abstract

Various traction devices have been developed to secure a visual field and sufficient tension at the dissection plane during endoscopic submucosal dissection (ESD). However, few large-scale studies have investigated the effectiveness of traction devices in gastric ESD. Clip-with-line (CWL) is one such traction device that is widely used in cases of gastric ESD. The CONNECT-G trial was the first multicenter randomized controlled trial to compare conventional ESD with CWL-assisted ESD (CWL-ESD) for superficial gastric neoplasms. Overall, no significant intergroup difference was observed in terms of the gastric ESD procedure time. However, subgroup analysis according to lesion location revealed a significant reduction in the procedure time of gastric ESD for the lesion located at the greater curvature of the middle and upper third of the stomach in the CWL-ESD group. In this subgroup analysis, lesion location was categorized as follows: anterior wall, posterior wall, lesser curvature, and greater curvature of the upper, middle, and lower thirds of the stomach. However, the gastric ESD procedure time showed no significant difference, except for lesions located at the greater curvature of the upper and middle thirds of the stomach. The traction direction of CWL in the stomach was limited to the cardia and changed depending on the lesion location. Therefore, outcomes of the CONNECT-G trail suggest that the effectiveness of CWL was influenced by lesion location, i.e., traction direction. Further studies are warranted to investigate the optimal traction direction in gastric ESD.

Key Words: Endoscopic submucosal dissection; ESD; Traction device; Clip-with-line; Traction direction; Vertical traction

Core Tip: Various traction devices have been developed for endoscopic submucosal dissection (ESD). However, few traction devices have been validated in large-scale studies thus far. The CONNECT-G trial was the first multicenter randomized controlled trial to compare conventional ESD with clip-with-line-assisted ESD for superficial gastric neoplasms. This study suggested that the effectiveness of traction devices in gastric ESD depends on the traction direction; in addition, the most optimal traction direction is vertical to the gastric wall.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) allows en bloc resection of superficial gastric neoplasms. However, gastric ESD is a challenging procedure. Surgeons can use their nondominant hand to generate traction for lesions while they resect using their dominant hand. Meanwhile, endoscopists cannot use their nondominant hand to generate traction because they cannot insert their hand into the stomach. Therefore, endoscopists occasionally cannot secure a visual field and sufficient tension at the dissection plane, resulting in a long ESD procedure time and a high perforation rate. Recently, many traction devices were reported to overcome these problems, but few large-scale studies investigated the effectiveness of traction devices in gastric ESD.

CONNECT-G TRIAL

The CONNECT-G trial was the first multicenter randomized controlled trial to compare conventional ESD with traction-assisted ESD for the treatment of superficial gastric neoplasms[1]. In this study, clip-with-line (CWL) was used as a traction device (Figure 1), and its traction direction is restricted to the direction where the line is drawn[2,3]. The primary endpoint was the mean gastric ESD procedure time, which was 58.1 min in the conventional ESD group and 60.7 min in the CWL-assisted ESD (CWL-ESD) group, with no significant difference (P = 0.45). R0 resection was not statistically significant in both groups (96.8% *vs* 97.8%, P = 0.45). However, the perforation rate was significantly lower in the CWL-ESD group (0.3% *vs* 2.2%, P = 0.04), suggesting that CWL may have improved the field of vision and reduced blind submucosal dissection.

For lesions located at the greater curvature of the middle and upper third of the stomach, the CWL-ESD group had a significantly shorter gastric ESD procedure time than the conventional ESD group (57.2 min *vs* 104.1 min, P = 0.01). This part of the stomach is a challenging area for conventional ESD because it is basically a gravitational lower side, so a mucosal flap is difficult to deploy, and the visual field tends to deteriorate due to fluid retention. Nevertheless, CWL-ESD is particularly useful in this area. In this subgroup analysis, lesion location was divided into the anterior wall, posterior wall, lesser curvature, and greater curvature of the upper, middle, and lower third of the stomach. However, no significant difference was found in the procedure time of gastric ESD, except for lesions located at the greater curvature of the middle and upper third of the stomach.

TRACTION DIRECTION OF CWL DIFFERS DEPENDING ON THE LESION LOCATION AND ENDOSCOPIC POSITION

The results of the CONNECT-G trail suggest that the effectiveness of CWL-ESD varies depending on the lesion location. Traction direction can be classified into five categories (Figure 2)[4]. Since CWL is a per-oral traction device, its traction direction is limited to the cardia and varies depending on the lesion location. Another consideration for the traction direction of CWL is the endoscopic position during submucosal dissection. Because of the large lumen of the stomach, there are two possible endoscopic positions: forward and retroflexed. Therefore, the traction direction also varies depending on the endoscopic position even if the lesion is in the same location. For example, for lesions located at the lesser curvature of the middle third of the stomach, CWL commonly provides a distal traction in retroflexed endoscopic position (Figure 3A) and proximal traction in forward endoscopic position (Figure 3B).

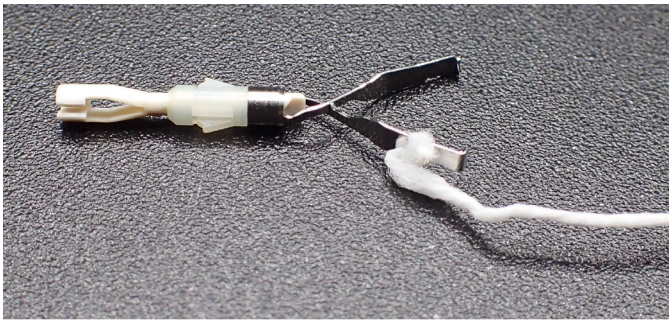

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Figure 1 A clip-with-line was made by tying a commercially available dental floss to the arm section of the hemoclip.

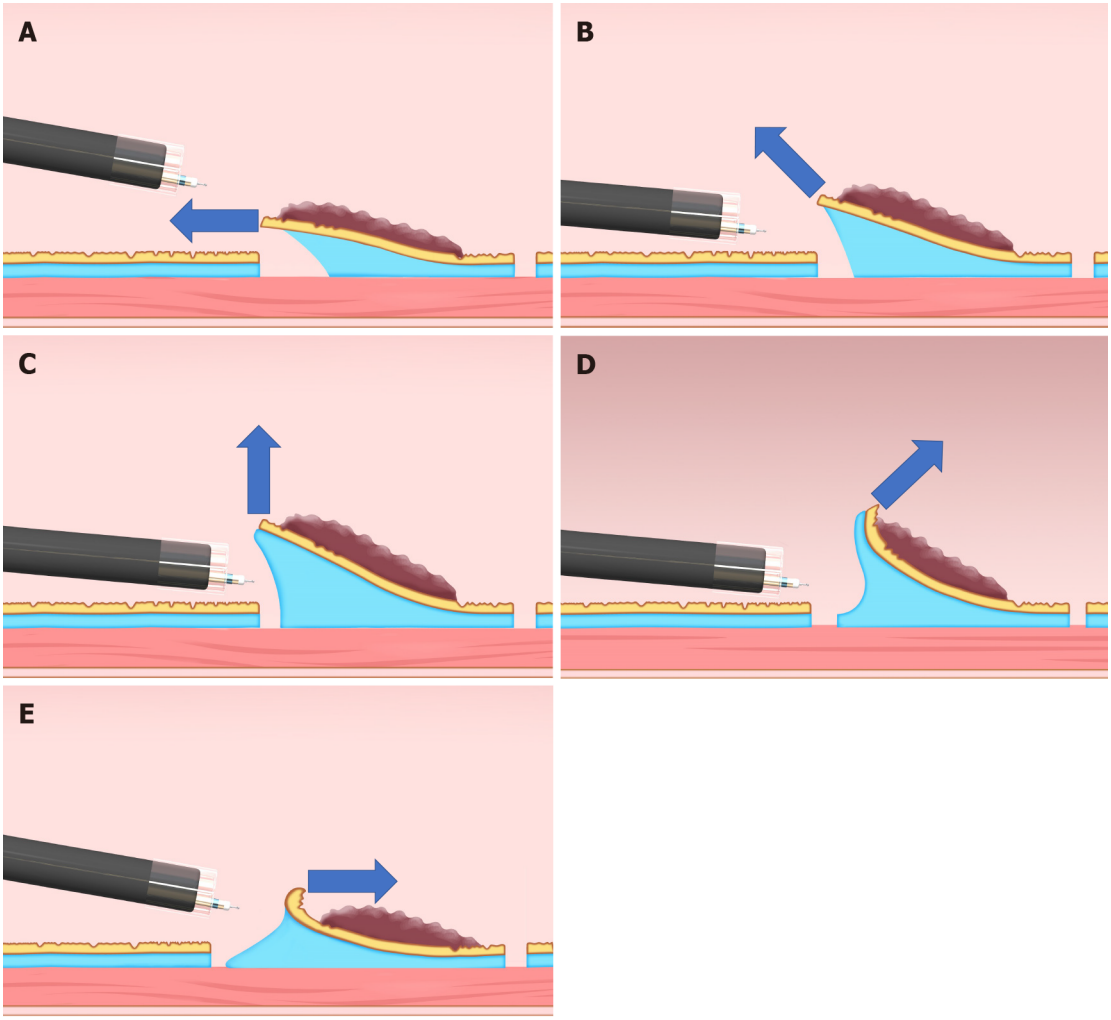

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Figure 2 Classification of the traction direction. A: Proximal traction; B: Diagonally proximal traction; C: Vertical traction; D: Diagonally distal traction; E: Distal traction. Citation: Reprinted from Mitsuru Nagata. Advances in traction methods for endoscopic submucosal dissection: What is the best traction method and traction direction? *World Journal of Gastroenterology* 2022; 28(1): 1–22. Copyright ©Mitsuru Nagata 2022. Published by Baishideng Publishing Group Inc.

WHAT IS THE OPTIMAL TRACTION DIRECTION IN GASTRIC ESD?

The optimal traction direction in gastric ESD was not yet fully investigated. However, several studies indicated that a vertical traction is the optimal traction direction. The CONNECT-G trial suggests that CWL is effective for lesions located at the greater curvature of the upper and middle third of the stomach, and vertical traction is frequently performed in this area from an anatomical point of view (Figure 3C). CWL can essentially only provide vertical traction for lesions located at the greater curvature of the stomach, but multidirectional traction devices, such as a spring-and-loop with clip

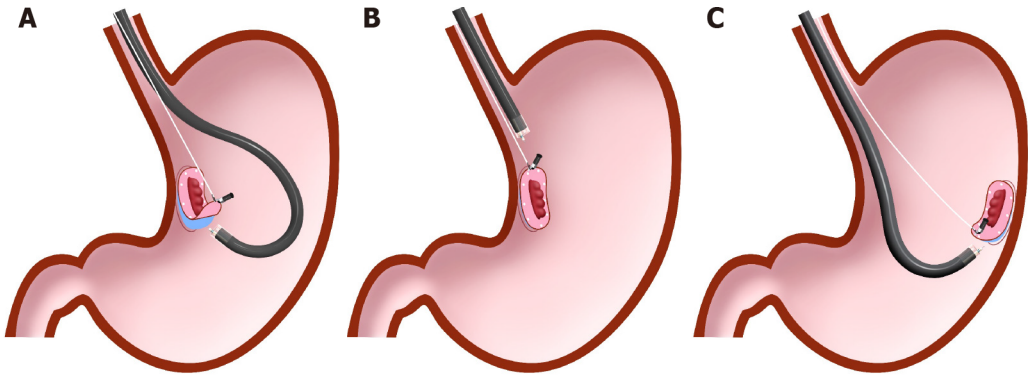

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Figure 3 Differences in traction direction depending on the lesion location in clip-with-line–assisted endoscopic submucosal dissection. A: Distal traction; B: Proximal traction; C: Vertical traction. Citation: Reprinted from Mitsuru Nagata. Advances in traction methods for endoscopic submucosal dissection: What is the best traction method and traction direction? *World Journal of Gastroenterology* 2022; 28(1): 1–22. Copyright ©Mitsuru Nagata 2022. Published by Baishideng Publishing Group Inc.

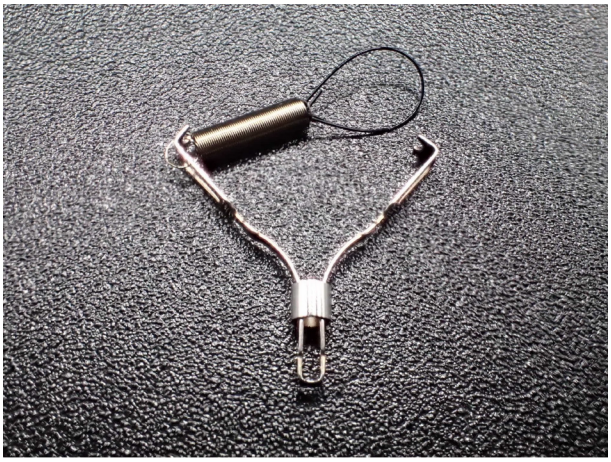

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Figure 4 An S–O clip (Zeon Medical, Tokyo, Japan) was made of a 5 mm-long spring and 4 mm-long nylon loop on one side of the clip claws.

(Figure 4; SLC; S–O clip; Zeon Medical, Tokyo, Japan), may provide a vertical traction for lesions in other areas. The SLC allows the traction direction to be controlled in any direction. This clip was developed as a traction device to provide traction for colorectal ESD. Hence, we have devised a novel usage of the SLC with both forward and retroflexed endoscopic positions for gastric ESD[5,6]. A single-center randomized controlled trial comparing conventional ESD and SLC-assisted ESD (SLC-ESD) was conducted. In SLC-ESD, a vertical traction was selected using the multidirectional traction function. This study demonstrated that the median gastric ESD procedure time was significantly shorter in SLC-ESD than in conventional ESD (29.1 min *vs* 52.6 min; $P = 0.005$)[7]. However, SLC-ESD was not associated with a reduction in the gastric ESD procedure time for lesions > 20 mm. As submucosal dissection progresses, the distance between the SLC attachment site and the anchor site diminishes gradually, resulting in weaker traction force due to the spring shortening. For larger lesions, diagonally proximal traction may be preferable to vertical traction to maintain spring extension even as submucosal dissection progresses or an additional SLC should be considered when traction force becomes weaker. Overall, considering the results of these two randomized controlled trials, vertical traction may be the optimal traction direction for most cases of gastric ESD.

It is unclear whether other traction directions are effective in gastric ESD. Especially in distal traction, as the submucosal dissection progresses, the dissection plane falls toward a distal direction, which may be counterproductive because it may not provide an effective tension on the dissection plane. In CWL-ESD, a retroflexed endoscopic position occasionally results in a distal traction, and this position is common in gastric ESD. It is possible that a distal traction was provided for a relatively large number of cases in the CONNECT-G trial, and this could cause no significant difference in gastric ESD procedure time between conventional ESD and CWL-ESD in the total population of the CONNECT-G trial. However, the traction direction and endoscopic position were not reported, so this point should be

further investigated.

In CWL-ESD, combined with the pulley method[8,9], the traction direction can be controlled, and vertical traction can be obtained. Therefore, the pulley method may improve the gastric ESD procedure time in CWL-ESD. However, since the pulley method in gastric ESD has been reported mainly in case series studies or *ex-vivo* studies, its feasibility and effectiveness should be further investigated.

CONCLUSION

Vertical traction may be the optimal traction direction in traction-assisted ESD for gastric neoplasms. Further studies are needed to investigate the effectiveness of other traction directions.

FOOTNOTES

Author contributions: Nagata M has been associated with the conception, drafting of the article, and final approval of the article.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Quality of colonoscopy performed by medical or surgical specialists and trainees in five Australian hospitals

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Abstract

BACKGROUND

Ensuring colonoscopy procedure quality is vital to the success of screening and surveillance programmes for bowel cancer in Australia. However, the data on the performance of quality metrics, through adequate adenoma detection, bowel preparation, and procedure completion rates, in the Australian public sector is limited. Understanding these can inform quality improvement to further strengthen our capacity for prevention and early detection of colorectal cancer.

AIM

To determine the quality of colonoscopy in Australian teaching hospitals and their association with proceduralist specialty, trainee involvement, and location.

METHODS

We retrospectively evaluated 2443 consecutive colonoscopy procedure reports from 1 January to 1 April, 2018 from five public teaching tertiary hospitals in Australia (median 60 years old, 49% male). Data for bowel preparation quality,

procedure completion rates, and detection rates of clinically significant adenomas, conventional adenomas, and serrated lesions was collected and compared to national criteria for quality in colonoscopy. Participating hospital, proceduralist specialty, and trainee involvement indicators were used for stratification. Data was analysed using Chi-squared tests of independence, Mann-Whitney *U*, One-way ANOVA, and multivariate binary logistic regression.

RESULTS

Fifty-two point two percent (n = 1276) and 43.3% (n = 1057) were performed by medical and surgical proceduralists respectively, whilst 29.8% (n = 728) involved a trainee. Inadequate bowel preparation affected 7.3% of all procedures. The procedure completion rate was 95.1%, which increased to 97.5% after adjustment for bowel preparation quality. The pooled cancer, adenoma, and serrated lesion detection rates for all five hospitals were 3.5%, 40%, and 5.9% respectively. Assessed hospitals varied significantly by patient age (P < 0.001), work-force composition (P < 0.001), adequacy of bowel preparation (P < 0.001), and adenoma detection rate (P < 0.001). Two hospitals (40%) did not meet all national criteria for quality, due to a procedure completion rate of 94.5% or serrated lesion detection rate of 2.6%. Although lower than the other hospitals, the difference was not significant. Compared with surgical specialists, procedures performed by medical specialists involved older patients [65 years (inter-quartile range, IQR 58-73) *vs* 64 years (IQR 56-71); P = 0.04] and were associated with a higher adenoma detection rate [odds ratio (OR) 1.53; confidence interval: 1.21-1.94; P < 0.001]. Procedures involving trainee proceduralists were not associated with differences in the detection of cancer, adenoma, or serrated lesions, compared with specialists, or according to their medical or surgical background. On multivariate analysis, cancer detection was positively associated with patient age (OR 1.04; P < 0.001) and negatively associated with medical compared to surgical proceduralists (OR 0.54; P = 0.04). Conventional adenoma detection rates were independently associated with increasing patient age (OR 1.04; P < 0.001), positively associated with medical compared to surgical proceduralists (OR 1.41; P = 0.002) and negatively associated with male gender (OR 0.53; P < 0.001).

CONCLUSION

Significant differences in the quality of colonoscopy in Australia exist, even when national benchmarks are achieved. The role of possible contributing factors, like procedural specialty and patient gender need further evaluation.

Key Words: Colonoscopy; Quality of health care; Adenoma detection rate; Bowel preparation quality; Hospital-based teaching

Core Tip: We evaluated the quality of colonoscopy performed at five teaching hospitals in Australia, using bowel preparation quality, procedure completion, and detection of cancer, adenoma, and serrated lesions as main indicators. In our retrospective analysis of 2443 procedures, the collective performance met national benchmarks for quality. However, two hospitals individually failed to meet all national benchmarks and we observed significant differences in key metrics of adenoma detection and adequacy of bowel preparation for colonoscopy across all hospitals. Higher adenoma detection rates were also independently shown amongst medical compared with surgical proceduralists, and amongst female patients.

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INTRODUCTION

Metrics conventionally used in the assessment of quality in colonoscopy are centred around its role in the prevention and early detection of colorectal cancer (CRC) and other gastrointestinal (GI) complications. These include the adenoma detection rate (ADR), generally considered the gold-standard indicator of quality, the adequacy of bowel cleansing and rate of procedure completion[1,2]. The im-

portance of the indicator to GI cancers screening and surveillance programs is highlighted by the association between lower ADRs and the development of interval cancers, whilst incomplete procedures or poor bowel preparation significantly increase the risk of subsequent advanced colonic lesions[3,4].

The Gastroenterological Society of Australia has recently implemented a recertification program using self-reported data to assess the performance of colonoscopy. Current nominated benchmarks include an ADR of 25% in eligible procedures, completion rate of at least 95% in patients with intact colons, and serrated lesion detection rate (SLDR) of 4%[5]. This can provide valuable data on adenoma detection, procedure completion, and bowel preparation rates. However, the data submitted for recertification typically relates to work performed for patients with private health insurance. This does not reflect the quality of procedures in government-funded universal healthcare, in which a quarter of all colonoscopies in Australia are performed[6]. Considering that patients of lower socio-economic background are not only at risk of the poorest outcomes of CRC and other GI complications, but are also reliant upon this pathway for access to healthcare, it is important to ensure its quality[6].

However, assessment of performance data from this section is limited to a handful of single-centre studies[7-10]. Furthermore, the quality of procedures performed by proceduralists-in-training in Australia remain unreported. Ensuring the quality of colonoscopy in this sector therefore also supports both current and future screening and surveillance practice. We measured the quality of colonoscopy performed in five public teaching hospitals in Australia. We aimed to assess not only the quality of the performed colonoscopies, but also key areas for further improvement and targeted solutions for potential problems.

MATERIALS AND METHODS

Study design and setting

We performed a retrospective, multicentre, cohort study across five hospitals (identified as Site 1-5) in South Australia and the Northern Territory with electronic records of colonoscopy and pathology data spanned over three months. Together, the catchment population for the five hospitals is estimated to be just over one million people. Ethical approval was granted by the Central Adelaide Local Health Network ethics committee.

Data collection

We searched GI endoscopy databases (ProVationMD) for colonoscopy procedures performed between 1 January, 2018 to 31 March, 2018 inclusive at each participating site. We excluded patients undergoing a flexible sigmoidoscopy, where only the left side of the colon was viewed. Patients younger than 18 years were also excluded as conventional quality metrics are not typically applied in the paediatric population. Endoscopy and linked pathology data was collected, anonymised, and managed using REDcap electronic data capture tools hosted at The University of Technology Sydney accessed through the Australian Access Federation[11,12].

We collected data including patient age, gender, proceduralist speciality, trainee participation, trainee specialty, and site for each procedure. We examined the records of each patient for a history of CRC, prior colonic resection, and inflammatory bowel disease (IBD). We evaluated the quality of bowel preparation according to the main validated scores used by the participating centres - either the Aronchick or the Boston Bowel Preparation Scale[13]. Histological diagnosis was confirmed by linked pathology reports accessed through site-specific electronic health records. Definitions for each outcome were outlined on the REDcap software to ensure consistency and quality in data collection amongst the authors.

Definitions

Adequacy of bowel preparation was defined by a description of fair, good, or excellent according to the Aronchick scale. Alternatively, a score of 6 or greater, with no individual segment less than 2, was used according to the Boston Bowel Preparation Scale[13]. The rate of inadequate bowel preparation was determined by the proportion of procedures which did not meet the above criteria when rated against either scale. The rate of indeterminate bowel preparation quality otherwise determined according to the proportion of procedures where an alternative or no scoring system was applied.

Procedure completion was defined by documented (either written or photographic) progress to the caecum or terminal ileum, in patients with an intact colon (the absence of a history of CRC or prior colonic resection). The procedure completion rate was defined by the proportion of procedures in which this was achieved. The adjusted procedure completion rate was defined by the proportion of colonoscopies with adequate bowel preparation where procedure completion was achieved.

We adapted conventional criteria for ADR to define the population (or eligible procedures) for which the detection rates for the various lesions (CRC, conventional adenomas, and serrated lesions) were determined. Typically this involves patients, aged 50 and over, who are undergoing their index colonoscopy following a positive bowel cancer screening test[14]. However, we also included procedures performed for other indications except for IBD and CRC or where prior colonic resection had occurred,

in line with definitions adopted nationally for recertification in colonoscopy[5]. Additionally, we excluded patients without adequate bowel preparation due to its impact on adenoma detection and its potential as a confounder.

The CRC detection rate was defined as the proportion of eligible procedures in which the cancer was identified and confirmed on histology. These cases were subsequently excluded for the calculation of detection rates for conventional adenomas and serrated lesions due to the possibility that a newly diagnosed CRC may influence proceduralists' further efforts to find and resect synchronous non-malignant lesions. The ADR and SLDR were thus defined by the proportion of procedures in which at least one conventional adenoma or serrated lesion respectively was identified on histology amongst the remaining procedures[15]. The clinically significant lesion detection rate (CSLDR) was determined according to the proportion of procedures where either a conventional adenoma, serrated lesion or both were identified amongst eligible procedures without a new CRC diagnosis.

Contemporary World Health Organisation histological definitions for conventional adenomas (tubular, tubulovillous, or villous adenoma) and serrated lesions (sessile serrated lesion, traditional serrated lesion or large hyperplastic polyp ≥ 10 mm) were used[16].

Assessment of outcomes

We determined the rates of inadequate bowel preparation and procedure completion for all hospitals, and stratified the results according to hospital, proceduralist specialty (medical/surgical), presence or absence of a trainee, and trainee specialty. Amongst eligible procedures, those with a new diagnosis were used to calculate the cancer detection rate. We analysed the remaining procedures to determine the ADR, SLDR, and CSLDRs. Lesions identified on colonoscopy without available histology were not counted when calculating detection rates. The detection rates for cancer, adenoma, serrated lesions, and clinically significant lesions were also stratified according to the same groups as above. We did not compare the outcomes of procedures performed by nurse endoscopists to those of medical or surgical specialists as they were only employed at a single hospital and thus subject to a significant risk of sampling bias.

The primary outcome was ADR. According to a recent meta-analysis showing an expected ADR of 40% with a confidence interval of 95% and a margin of error of 5%, we assessed a minimum sample of 369 patients[17].

Statistical analysis

Descriptive statistics was adapted to characterise the data. Chi-squared tests of independence were used to analyse nominal data. Mann-Whitney *U* test and one-way ANOVA tests were used for comparison of non-parametric data. Multivariate binary logistic regression was used to determine contributing factors for detection rates for cancer, adenomas, and serrated lesions. The significance level was set at 0.05. IBM SPSS Statistics version 27 was used.

RESULTS

A total of 2443 consecutive colonoscopies were performed from January to April of 2018. 49% (n = 1198) of the patients were male with a median age of 60 (inter-quartile range 50-70). Prior to exclusions, 69.1% (n = 1688) of procedures were performed on individuals aged 50 or greater; 6.4% (n = 156) of procedures were indicated for a personal history of CRC; 7.9% (n = 192) had undergone prior surgical resection; and 6.5% (n = 159) of procedures were indicated for IBD. Bowel preparation was documented as adequate in 86.9% (n = 2123), indeterminate in 5.8% (n = 142), and inadequate in 7.3% (n = 178) of procedures, respectively. Procedure completion was confirmed in 95.1% (n = 2114) after 9% (n = 220) of procedures were excluded for either a history of CRC or prior surgical resection. After excluding additional procedures for inadequate or indeterminate bowel preparation quality (n = 288), the adjusted procedure completion rate was 97.5%.

Of the total 2443 procedures, we excluded 600 that were conducted in patients under 50 years old; and a further 74 with IBD; 137 with CRC; 34 with prior bowel surgery; 77 incomplete procedures; and 181 with inadequate or indeterminate bowel preparations (Figure 1). Consequently, 1340 (54.9%) procedures were considered eligible for the determination of detection rates for cancer, conventional adenomas, and serrated lesions. Cancer was detected in 1.9% (n = 47) of patients. Conventional adenomas and serrated lesions were identified in 40% (n = 517) and 5.9% (n = 76) of the remaining procedures, respectively.

Our analysis indicated that 43.3% (n = 1057) and 52.2% (n = 1276) of procedures were performed by surgical and medical specialty groups, respectively. Nurse endoscopists conducted 4.5% (n = 106) of procedures at a single site. The specialty could not be determined in the remaining four cases where a proceduralist was not named on the colonoscopy report. Amongst all procedures, 29.8% (n = 728) of colonoscopies were attended by trainees. Of these, 45.9% (n = 334) of procedures were attended by a medical trainee.

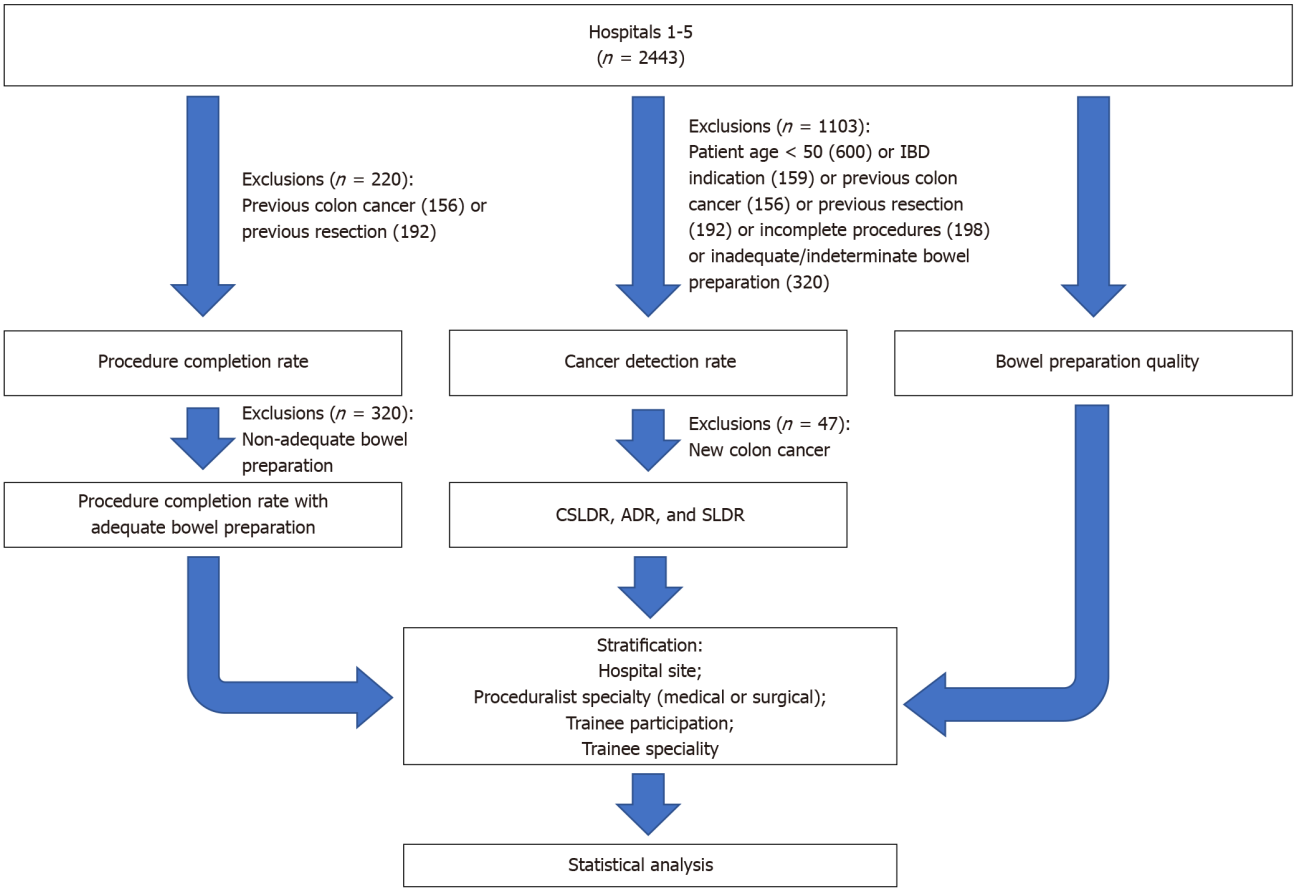

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Figure 1 Study flow chart. IBD: Inflammatory bowel disease; CSLDR: Clinically significant lesion detection rate; ADR: Adenoma detection rate; SLDR: Serrated lesion detection rate.

On analysing outcomes according to specialty group, a total of 551 eligible procedures were performed by surgical proceduralists, with cancer detected in 4.7% (n = 26) of cases (Table 1). Of the remaining procedures, conventional adenomas and serrated lesions were identified in 34% (n = 178) and 4.6% (n = 24) respectively. In comparison, 716 eligible procedures were performed by medical proceduralists, with cancer detected in 2.7% (n = 19) of cases. After excluding new diagnoses of cancer, medical proceduralists identified conventional adenomas and serrated lesions in 44% (n = 307) and 6.6% (n = 46).

Further analysis indicated that, compared with medical specialists, surgeons performed their procedures on a significantly younger patient group (P = 0.04). The overall cancer detection rate was lower among medical compared to surgical specialists, although the difference was not found to be significant (P = 0.052). The odds of detecting a clinically significant polyp or adenoma, however, were significantly higher amongst medical than surgical specialists [P < 0.001, odds ratio (OR) 1.58, (95% confidence interval (CI): 1.25-1.99); P < 0.001, OR 1.53, (95%CI: 1.21-1.94)] (Table 1).

When we compared 370 eligible procedures performed with trainees present against 968 performed by specialists, no significant differences in the cancer, adenoma, and serrated lesion detection rates were found (Table 2). Similarly, no significant differences in the lesion detection rates were found amongst the procedures attended by trainees according to their background specialty (Table 3).

Following this, sites were compared for the quality of endoscopic procedures. Prior to exclusions (n = 2443), there were significant variations in the age of patients undergoing colonoscopy (P < 0.001); the procedure completion rate (P < 0.001); proportion of procedures performed by surgical or medical proceduralists (P < 0.001); degree of trainee involvement (P < 0.001); and bowel preparation quality (P < 0.001) (Table 4). Following univariate analysis, significant differences were observed in the detection of conventional adenomas (P = 0.01) and clinically significant polyps (P = 0.01), but not for cancer (P = 0.38) or serrated lesions (P = 0.31).

However, some differences were found to be no longer significant when multivariate analysis was performed (Tables 4 and 5). Our analysis indicates that two factors were associated with cancer detection: increasing patient age, and procedures performed by surgical specialists (Tables 4 and 5). Adenoma detection was increased with increasing patient age, female gender, and procedures performed by medical proceduralists. We also observed a trend towards the increased detection of serrated lesions amongst male patients, but this did not reach the significance level (P = 0.054).

Table 1 Comparison of key outcomes between eligible procedures performed by medical and surgical specialists

	Medical, *n* = 716	Surgical, *n* = 551	*P* value	OR (95%CI)
Patient age, median (IQR)	65 (58-73)	64 (56-71)	0.04	-
Patient gender (male %)	49.7 (*n* = 356)	48.8 (*n* = 269)	0.75	-
Cancer detection rate (%)	2.7 (*n* = 19)	4.7 (*n* = 26)	0.052	0.55 (0.30-1.01)
CSPDR (%)	46.6 (*n* = 325)	35.6 (*n* = 187)	< 0.001	1.58 (1.25-1.99)
ADR (%)	44 (*n* = 307)	34 (*n* = 178)	< 0.001	1.53 (1.21-1.94)
SLDR (%)	6.6 (*n* = 46)	4.6 (*n* = 24)	0.13	1.47 (0.89-2.45)

CSPDR: Clinically significant polyp detection rate; ADR: Adenoma detection rate; SLDR: Serrated lesion detection rate; CI: Confidence interval; OR: Odds ratio; IQR: Inter-quartile range.

Table 2 Comparison of outcomes between eligible procedures performed with and without trainees

	With trainees, *n* = 370	Without trainees, *n* = 968	*P* value	OR (95%CI)
Patient age, median (IQR)	64 (57-72)	64 (57-72)	0.83	-
Patient gender (male %)	53.5 (*n* = 198)	47.4 (*n* = 463)	0.06	-
Cancer detection rate (%)	4.1 (*n* = 15)	3.3 (*n* = 32)	0.51	1.24 (0.66-2.31)
CSPDR (%)	41.4 (*n* = 147)	42.7 (*n* = 400)	0.67	0.95 (0.74-1.21)
ADR (%)	38.9 (*n* = 138)	40.4 (*n* = 378)	0.62	0.94 (0.73-1.21)
SLDR (%)	4.8 (*n* = 17)	6.3 (*n* = 59)	0.30	0.74 (0.43-1.30)

CSPDR: Clinically significant polyp detection rate; ADR: Adenoma detection rate; SLDR: Serrated lesion detection rate; CI: Confidence interval; OR: Odds ratio; IQR: Inter-quartile range.

Table 3 Comparison of outcomes between eligible procedures performed with medical and surgical trainees

	Medical trainees, *n* = 370	Surgical trainees, *n* = 968	*P* value	OR (95%CI)
Patient age, median (IQR)	59.5 (47-71)	59 (48.75-69)	0.30	-
Patient gender (male %)	49.7 (*n* = 166)	52.3 (*n* = 206)	0.49	-
Cancer detection rate (%)	2.3 (*n* = 5)	3.3 (*n* = 10)	0.49	0.68 (0.23-2.02)
CSPDR (%)	38.2 (*n* = 81)	32.5 (*n* = 94)	0.19	1.28 (0.89-1.86)
ADR (%)	36.3 (*n* = 77)	29.1 (*n* = 84)	0.09	1.39 (0.95-2.03)
SLDR (%)	5.7 (*n* = 12)	5.2 (*n* = 15)	0.82	1.1 (0.5-2.39)

CSPDR: Clinically significant polyp detection rate; ADR: Adenoma detection rate; SLDR: Serrated lesion detection rate; CI: Confidence interval; OR: Odds ratio; IQR: Inter-quartile range.

DISCUSSION

Although heterogeneity of colonoscopy practice in Australia has been previously described, there are limited reports about its quality, or its association with proceduralist specialty or the involvement of trainees[6]. To our knowledge, this is the first paper to assess quality outcome measures in colonoscopy for surgical and medical specialists, and their trainees across multiple Australian hospitals.

While the collective rates for lesion detection, procedure completion, and adequacy of bowel preparation all met national criteria for quality in colonoscopy, this was only achieved at three sites independently. Limited rates of procedure completion and detection of serrated lesions affected the remaining two sites. When these key metrics were compared between hospitals, however, no significant differences were detected. This discrepancy may be explained by the comparatively low sample sizes at these individual sites with correspondingly wide confidence intervals. It is likely that individuals might be susceptible to the same issue given that submissions for recertification in Australia only require data

Table 4 Comparison of key outcomes between participating hospitals

	Site 1 (*n* = 254)	Site 2 (*n* = 396)	Site 3 (*n* = 604)	Site 4 (*n* = 790)	Site 5 (*n* = 399)	*P* value	Overall (*n* = 2443)
Patient age, median (IQR)	56 (46-66)	61 (50-71)	59.5 (49-70)	61 (50-71)	60 (50-71)	< 0.001	60 (50-70)
Patient gender (male %)	56.7 (*n* = 144)	45.7 (*n* = 181)	48.0 (*n* = 290)	48.4 (*n* = 382)	50.4 (*n* = 201)	0.08	49.0 (*n* = 1197)
Proceduralist							
Surgical (%)	87.4 (*n* = 222)	33.1 (*n* = 131)	35.6 (*n* = 215)	35.9 (*n* = 284)	51.4 (*n* = 205)	< 0.001	43.3 (*n* = 1057)
Medical (%)	12.6 (*n* = 32)	66.9 (*n* = 265)	64.1 (*n* = 387)	50.5 (*n* = 399)	48.4 (*n* = 193)	< 0.001	52.2 (*n* = 1276)
Trainee (%)	59.4 (*n* = 151)	38.9 (*n* = 154)	8.1 (*n* = 49)	28.1 (*n* = 222)	38.1 (*n* = 152)	< 0.001	29.8 (*n* = 728)
Medical (%)	0 (*n* = 0)	61.7 (*n* = 95)	91.8 (*n* = 45)	39.2 (*n* = 87)	70.4 (*n* = 107)	-	45.9 (*n* = 334)
Surgical (%)	100 (*n* = 151)	38.3 (*n* = 59)	8.2 (*n* = 4)	60.8 (*n* = 135)	29.6 (*n* = 45)	-	54.1 (*n* = 394)
Inadequate bowel preparation (%)	13.4 (*n* = 34)	8.1 (*n* = 32)	2.6 (*n* = 16)	7.2 (*n* = 57)	9.8 (*n* = 39)	< 0.001	7.3 (*n* = 178)
Indeterminate bowel preparation (%)	0.0 (*n* = 0)	2.8 (*n* = 11)	1.5 (*n* = 9)	4.3 (*n* = 34)	22.1 (*n* = 88)	< 0.001	5.8 (*n* = 142)
Procedure completion (%)	94.3 (*n* = 215)	92.2 (*n* = 319)	98.2 (*n* = 556)	95.1 (*n* = 686)	93.4 (*n* = 338)	< 0.001	95.1 (*n* = 2114)
Procedure completion (%) with adequate preparation	98.0 (*n* = 195)	94.5 (*n* = 294)	99.2 (*n* = 537)	98.0 (*n* = 627)	96.3 (*n* = 233)	0.99	97.5 (*n* = 1886)
Eligible procedures	121	216	381	462	160		1340
Cancer detection (%)	5.0 (*n* = 6)	2.3 (*n* = 5)	2.9 (*n* = 11)	3.5 (*n* = 16)	5.6 (*n* = 9)	0.38	3.5 (*n* = 47)
CSPDR (%)	30.4 (*n* = 35)	40.8 (*n* = 86)	48.6 (*n* = 180)	42.6 (*n* = 190)	41.1 (*n* = 62)	0.01	42.8 (*n* = 553)
ADR (%)	27.8 (*n* = 32)	39.3 (*n* = 83)	45.7 (*n* = 169)	39.5 (*n* = 176)	37.7 (*n* = 57)	0.01	40.0 (*n* = 517)
SLDR (%)	2.6 (*n* = 3)	5.2 (*n* = 11)	5.1 (*n* = 19)	7.4 (*n* = 33)	6.6 (*n* = 10)	0.31	5.9 (*n* = 76)

CSPDR: Clinically significant polyp detection rate; ADR: Adenoma detection rate; SLDR: Serrated lesion detection rate; IQR: Inter-quartile range.

from as few as 150 procedures. Although statistical comparisons with peers could provide an alternative method of assessment in this setting, the outcome ultimately requires further study with longer sampling times for low-volume centres.

One area where hospital sites differed significantly was in the quality of bowel preparation. The importance of this metric is attributable to its association with ADR and procedure completion[2,18]. The rates of inadequate preparation within our analysis were comparable with the 9%-13% previously observed in two Australian studies[19,20]. A validated scale for bowel preparation quality (Boston Bowel Preparation or Aronchick), however, was only adopted in one of these[19]. Although either scale was used in 94.2% of colonoscopy procedures assessed in our study, unvalidated approaches were used in up to 22.1% of procedures at individual sites. The exclusion of these procedures from the calculation of completion and detection rates may have been a significant source of bias, potentially limiting our analysis. Considering that suboptimal bowel preparations also justify the re-booking of procedures, ensuring the standardised adoption of validated scales in participating centres should be a priority for quality assurance.

The ADR across all sites in our study comfortably surpassed national benchmarks for quality. Although this was similar to rates reported in a recent meta-analysis of the international literature, direct comparisons should be interpreted with caution due to differences in the definitions used in our study[17]. Whilst ADR has traditionally been determined amongst patients over 50 undergoing an index colonoscopy for the indication of a positive bowel cancer screening test, we included all indications except IBD or prior colorectal surgery as per our national recertification program. However, we additionally excluded non-adequate bowel preparation and incomplete procedures so that the ADR might be a more accurate indicator of technical proficiency. Consequently, this would allow for quality improvement initiatives to be better targeted. Although ADR differed between sites, this was no longer significant on multivariate analysis.

Both patient and proceduralist factors can affect adenoma and lesion detection rates[21]. The medical proceduralists in our study demonstrated significantly higher ADRs compared to their surgical counterparts on both univariate ($P < 0.001$) and multivariate analyses ($P = 0.002$). The area is controversial with two other Australian studies reporting conflicting results. Lee *et al*[10] found no difference in ADR amongst 300 procedures completed by medical or surgical specialists in a single centre, whilst Zorron Cheng Tao Pu *et al*[8] showed a significantly higher ADR, of 36.8% and 30.4% ($P < 0.001$), amongst medical proceduralists. Our findings are, however, consistent with a recent meta-analysis of 36

Table 5 Multivariate regression analysis for detection rates of cancer, adenomas, and serrated lesions amongst eligible procedures

	Coefficient	OR (95%CI)	*P* value
Cancer			
Site	0.11	1.11 (0.87-1.43)	0.40
Patient age	0.04	1.04 (1.02-1.07)	< 0.001
Patient gender (male)	-0.45	0.64 (0.36-1.14)	0.13
Trainee (present)	-0.12	0.89 (0.46-1.73)	0.73
Proceduralist (medical)[1]	-0.61	0.54 (0.30-0.97)	0.04
Adenomas			
Site	-0.01	0.99 (0.90-1.09)	0.84
Patient age	0.04	1.04 (1.03-1.05)	< 0.001
Patient gender (male)	-0.65	0.53 (0.42-0.65)	< 0.001
Trainee (present)	0.22	1.24 (0.96-1.61)	0.10
Proceduralist (medical)[1]	0.34	1.41 (1.13-1.76)	0.002
Serrated lesions			
Site	0.08	1.08 (0.90-1.3)	0.42
Patient age	0.00	1.00 (0.99-1.02)	0.57
Patient gender (male)	0.41	1.51 (0.99-2.29)	0.05
Trainee (present)	0.26	1.29 (0.78-2.14)	0.33
Proceduralist (medical)[1]	0.28	1.32 (0.87-2.02)	0.19

[1]Surgical specialists were defined as the reference population.
CI: Confidence interval; OR: Odds ratio.

international studies which reported results which were similar to ours[22]. This raises important questions about whether the patients of surgical specialists are disadvantaged. However, the possibility of selection bias due to additional factors which influence ADR, such as procedure indication, should be considered[23]. Additional studies to understand the difference between medical and surgical specialists in Australia are thus required.

A higher cancer detection rate amongst surgical specialists was also observed in our multivariate analysis. Although such a finding would appear to contradict the lower ADR, it would most likely reflect a selection bias in the process of referral for colonoscopy. We assumed that patients with more conspicuous CRC diagnoses would more likely be referred to a surgical specialist. However, data on referral indication was not available in this dataset.

Another key finding of the multivariate analysis was the association between gender and ADR. Higher adenoma detection and CRC risk are usually seen in men and thus the finding of increased adenoma detection amongst female patients was unexpected[24,25]. Metabolic risk factors which increase the risk of adenoma development, including smoking, alcohol use, and low physical activity, have however been observed more frequently in women[26,27]. However, data on these lifestyle factors was not available. On the other hand, our findings may alternatively suggest better engagement of females in individuals with increased risk of adenoma and CRC development. Further studies to validate these results and understand the mechanism of increased ADR amongst women in Australia are therefore also required.

No significant differences were found in the primary outcomes between trainee and specialist proceduralists, the detection of serrated lesions, or procedure completion after adjustment for bowel preparation. Further analysis of trainees according to background speciality similarly showed no significant differences. Together, these findings suggest that the quality of procedures involving training proceduralists are comparable to those of specialists. These findings encouraging for patients who may have reservations about the quality of their procedures on teaching lists within the public sector in Australia. As the next generation of proceduralists in Australia, it is vital that good quality colonoscopy is a foundation of their clinical practice.

Limitations

The sample size at each individual site may be considered as a limitation of the current study which

incorporated five study sites (hospitals). Although the included sites represent both regional and metropolitan practice across two states and territories, it may not be reflective of the broader picture of public practice. To our knowledge, however, it is the first and largest multicentre dataset analysis providing an insight into the quality of colonoscopy in training hospitals in Australia.

One of the major limitations of this study is its retrospective design. Indeterminate outcomes resulting from shortfalls in the quality of the documentation were censored from the analyses but could have affected the results. Non-validated bowel preparation quality scoring systems could not be interpreted although it would have been expected that inadequate preparations would have been reported as such. Limited documentation of withdrawal times also meant that this could not be measured within this study, despite its accepted place as a marker of procedure quality. A prospective study design could account for these limitations and may provide more data reliable quality of documentation, however, would be susceptible to bias from the Hawthorne effect[28].

The exclusions for calculating key metrics in this study also differs from those used in prior studies or the National Recertification program[5,29]. Although this may limit the ability to compare the outcomes against national and internationally reported metrics, we would argue that the adjustments allow the metrics to reflect the aspects of practical interest more accurately. Our definitions separated the outcomes of procedure completion, quality of bowel preparation, and lesion detection which can inform targeted quality improvement efforts. This could include split preparations and shorter runway times to improve quality of bowel preparation, technical re-training for issues associated with procedure completion, or monitoring of withdrawal times for lesion detection. Caution should be taken in the assessment of lesion detection rates however due to the incorporation of multiple indications (screening; surveillance; symptomatic presentations) in the definition of the eligible population.

The definition for serrated lesions adopted within this study were in line with the most recent World Health Organization publication[16]. Repeated updates to these definitions have resulted in the reclassification of lesions in prior studies and remain dependent on the expertise of the reporting pathologist. The absence of a centralised expert pathologist for the assessment of resected lesions of the bowel may have resulted in the misclassification of some lesions, particularly serrated ones. Although we detected no differences in the detection of serrated lesions in our study, it is possible that this may have been masked by misclassification. Careful consideration of the definitions employed in colonoscopy is required for the interpretation of quality outcomes.

Despite potential limitations, our study offers novel clinical insights into the quality of procedures currently being performed in Australian public hospitals. These results highlight the need for quality procedural reporting and bowel preparation, as well as further research into factors which may result in lower ADRs amongst surgeons and men.

CONCLUSION

Our study indicates that the quality of colonoscopy collectively in the Australian public sector meets national benchmarks. Even when national benchmarks targets were achieved, significant differences in the quality of bowel preparation, and ADRs according to proceduralist specialty and patient gender were found. Two sites of the five assessed did not individually meet all the requirements. Improving bowel preparation should therefore be a key target for quality improvement initiatives. Our analysis suggested that sampling bias was a significant contributing factor which requires attention and control in future investigations. Additional studies to understand why surgical proceduralists detect fewer adenomas than their medical counterparts, and why women in Australia have higher rates of adenoma are required.

ARTICLE HIGHLIGHTS

Research background

There is increasing attention on the quality of colonoscopy performed in Australia due to its vital role in the prevention of colorectal cancer, and its relative under-utilisation among rural and lower socioeconomic communities. However, quality of colonoscopy in Australia has seldom been reported outside of single-centre studies. The largest database, the National Re-certification Program, attempts to address this but largely reflects the quality of work being performed in private hospital settings. Government funded procedures are not well represented in this data, yet accounts for 25% of colonoscopy work, and remains the main pathway for patients without private insurance and within the lowest socioeconomic strata to access this care. We sought to characterise the quality of colonoscopy in this sector, with the aim of informing quality improvement initiatives.

Research motivation

The key quality metrics for colonoscopy are bowel preparation quality, procedure completion rate, and

lesion detection rates (cancer, adenomas, and clinically significant serrated lesions). Serrated lesions have also received increasing attention recently, resulting in their incorporation within current national re-certification guidelines. We hope to determine if there are deficiencies in these metrics according to national guidelines and by comparison between participating hospital sites. We also sought to determine if there are significant differences in the detection rates of lesions according to consultant specialty (medical *vs* surgical), training level (specialist *vs* trainee), hospital site, and trainee background (medical *vs* surgical). The outcomes of this research can drive further inquiry into understanding the reasons for these differences and potential solutions.

Research objectives

We aimed to determine the lesion (cancer, adenoma, clinically significant serrated lesion) detection rates, quality of bowel preparation, procedure completion rates among teaching hospitals in Australia. Additionally, we wished to compare the outcomes according to proceduralist specialty, hospital, involvement of trainees, and trainee specialty. We were able to realize all these outcomes, however the analysis of outcomes according to sites was limited by the small sample sizes at some of the participating hospitals. Further studies to explore the link between proceduralist specialty, gender, and adenoma detection rates in Australia are warranted. Additional research regarding methods to improve these outcomes is also indicated.

Research methods

This was a retrospective cohort study involving consecutive colonoscopies performed over five publicly-funded teaching hospitals in Australia. Currently available colonoscopy quality metrics in Australia are either self-reported and reflect privately funded procedural work or pertain to fewer procedures at single centres. To our knowledge, this is the first study to describe colonoscopy quality across multiple large teaching endoscopy units in the public sector of Australia.

Research results

The overall quality of colonoscopy performed in participating hospitals met all specified national benchmarks (adenoma detection rate/procedure completion rate/serrated lesion detection rate). Two hospitals did not meet all benchmarks, due to either a low procedure completion or serrated lesion detection rate, when assessed individually. However, these results were not significantly different when compared with their peers. Significant differences between hospitals were identified on the remaining outcomes of bowel preparation, and detection of cancers and adenomas. Medical specialists detected adenomas in significantly more procedures than their surgical counterparts. In procedures attended by trainees, the detection rate of clinically significant lesions (cancer, adenoma, serrated lesions) was no different to those only involving specialists. Trainee specialty similarly did not affect lesion detection rates. The difference in adenoma detection rate between medical and surgical specialists was confirmed on multivariate analysis. An additional unexpected finding on the multivariate analysis was an association between female gender and adenoma detection. The findings highlight the need for further research to understand the differences between the colonoscopy procedures performed by medical and surgical specialists, and the reasons why female gender in this cohort of patients was an independent risk factor for adenoma detection. Furthermore, it suggests the need for additional sampling in lower-volume endoscopy units for the assessment of quality in colonoscopy.

Research conclusions

Our study suggests that although the overall quality of colonoscopy in publicly funded Australian hospitals reach national standards, significant variations exist between hospitals, according to procedural specialty, as well as patient gender. Understanding the reasons for these differences can provide additional insights on how quality in colonoscopy can be further improved. Although comparison with peer hospitals may provide an acceptable alternative for the assessment of outcomes in low-volume centres, larger studies are ideally required to assess their quality independently.

Research perspectives

Further research is required to explain the disparity in adenoma detection rates between medical and surgical specialists performing colonoscopy, and to determine why female, rather than male gender, is an independent predictor for adenoma in Australia.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Effectiveness and safety of endoscopic resection for duodenal gastrointestinal stromal tumors: A single center analysis

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Abstract

BACKGROUND

Endoscopic resection for duodenal gastrointestinal stromal tumors (GISTs) is still considered a great challenge with a high risk of complications, including perforation, bleeding, tumor rupture, and residual tumor.

AIM

To assess the effectiveness and safety of endoscopic resection for duodenal GISTs.

METHODS

Between January 2010 and January 2022, 11 patients with duodenal GISTs were treated with endoscopic resection. Data were extracted for the incidence of complete resection, bleeding, perforation, postoperative infection, recurrence, and distant metastasis.

RESULTS

The incidence of successful complete resection of duodenal GISTs was 100%. Three cases (27.3%) had suspected positive margins, and the other 8 cases (72.7%)

had negative vertical and horizontal margins. Perforation occurred in all 11 patients. The success rate of perforation closure was 100%, while 1 patient (9.1%) had suspected delayed perforation. All bleeding during the procedure was managed by endoscopic methods. One case (9.1%) had delayed bleeding. Postoperative infection occurred in 6 patients (54.5%), including 1 who developed septic shock and 1 who developed a right iliac fossa abscess. All 11 patients recovered and were discharged. The mean hospital stay was 15.3 d. During the follow-up period (14-80 mo), duodenal stenosis occurred in 1 case (9.1%), and no local recurrence or distant metastasis were detected.

CONCLUSION
Endoscopic resection for duodenal GISTs appears to be an effective and safe minimally invasive treatment when performed by an experienced endoscopist.

Key Words: Duodenal tumor; Gastrointestinal stromal tumors; Treatment; Endoscopic resection; Effectiveness; Safety

Core Tip: This study presents the findings on endoscopic resection for duodenal gastrointestinal stromal tumors. Endoscopic resection of duodenal gastrointestinal stromal tumors is a great challenge. This study aimed to assess the effectiveness and safety of endoscopic resection for duodenal gastrointestinal stromal tumors. The rate of successful complete resection was 100%. Intraoperative perforation occurred in all 11 patients. The success rate of perforation closure was 100%. All 11 patients recovered. During the follow-up period (14-80 mo), duodenal stenosis occurred in 1 case (9.1%), and no local recurrence or distant metastases were detected.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are rare digestive mesenchymal tumors, characterized by differentiation towards the interstitial cells of Cajal[1]. They can occur in any part of the gastrointestinal tract, most commonly in the stomach (60%) and small intestine (30%), but only 4%-5% occur in the duodenum [2]. GISTs have a variety of clinical behaviors with potentially malignant tendency. Currently, the treatment strategy for GISTs is somewhat controversial[3]. Some studies show that active surveillance was a safe option for GISTs smaller than 20 mm or even 30 mm (excision is only considered when the tumor grows)[4,5]. However, GISTs have inherent potential for malignancy, and the real risk stratification of the lesions is only known after resection[6]. Therefore, several societies recommend resection if a diagnosis of GIST is made, unless a major morbidity is expected[7-9].

In comparison to gastric GISTs, duodenal GISTs have a higher risk of malignancy. In addition, the duodenum has special anatomical features. Once the tumor grows, the difficulty of the operation increases accordingly, increasing the risk of combined organ resection. Therefore, resection should be performed for localized or potentially resectable duodenal GISTs. Traditional surgical treatment methods include pancreaticoduodenectomy and local resection of duodenal lesions. However, these operations are traumatic and prone to serious complications, such as delayed bleeding, pancreatic leakage, bile leakage, or abdominal infection[10,11]. Furthermore, pancreaticoduodenectomy or segmental duodenectomy will inevitably reduce the patient's quality of life. GISTs have unique biological characteristics and rarely have lymph node metastasis[9], which makes endoscopic resection of lesions an alternative. In recent years, the development of endoscopic minimally invasive technologies, such as endoscopic submucosal dissection, endoscopic submucosal excavation, and endoscopic full-thickness resection, has brought attention to endoscopic minimally invasive treatment of duodenal GISTs.

Thus far, there are few studies about endoscopic resection of duodenal GISTs, most of which have been case reports. A few studies have reported small series of cases[12,13]. The aim of this study was to evaluate the effectiveness and safety of endoscopic resection for duodenal GISTs.

MATERIALS AND METHODS

Patients

From January 2010 to January 2022, 11 consecutive patients with pathologically confirmed duodenal GIST underwent endoscopic resection in our center. All patients were examined preoperatively by computed tomography (CT) and endoscopic ultrasonography (EUS). In all cases, there were no signs of lymph node metastasis or distant metastasis, no other malignant tumors, and no coagulation dysfunction, and it was considered that the patient could tolerate endotracheal intubation and general anesthesia. Written informed consent was obtained from all patients. The study was reviewed and approved by the Institutional Ethics Committee of Taizhou Hospital of Zhejiang Province (Approval No. K20210611).

Endoscopic equipment and accessories

A single-accessory channel endoscope (Q260J; Olympus) and/or a dual-channel endoscope (GIF-2T240, Olympus) were used during the procedures. A transparent cap (ND-201-11802; Olympus) was attached to the tip of the endoscope. An insulated-tip knife (KD-611L, IT2; Olympus), hook knife (KD-620LR; Olympus), dual knife (KD-650Q; Olympus), or hybrid knife (ERBE, Tübingen, Germany) was used to dissect the submucosal layer and peel the tumor. A titanium clip (HX-600-135; Olympus and M00522600), an endoloop (Leo Medical Co., Ltd, Changzhou, China), and an over-the-scope clip (OTSC) (12/6 t-type, Ovesco Endoscopy AG) were used for wound closure. Other devices and accessories that were used included a high-frequency electronic cutting device (ICC 200; ERBE), an argon plasma coagulation unit (APC 300; ERBE, Tübingen, Germany), a hot biopsy forceps (FD-410LR; Olympus), a foreign body forceps (FG-B-24, Kangjin, Changzhou, China), a snare (SD-230U-20; Olympus), and a carbon dioxide insufflator (Olympus).

Endoscopic procedures and perioperative management

All operations were performed under general anesthesia with endotracheal intubation by experienced endoscopists. All patients were fasted for ≥ 6-8 h with no water for 2 h before the operation. Antibiotic prophylaxis was administered.

Endoscopic resection was conducted as follows (Figure 1A-K): (1) Several dots were marked around the lesion; (2) A mixture solution (100 mL normal saline +1 mL epinephrine + 2 mL indigo carmine) was then injected to elevate the submucosa; (3) Subsequently, a circumferential incision was made outside the border to expose the pseudo capsule; (4) Next, the submucosa and muscularis propria (MP) around the lesion were circumferentially dissected. After complete excision, the lesion was removed with a snare or foreign body forceps and sent for histopathological examination; and (5) The wound was closed with titanium clips, an OTSC, or an endoloop. If perforation occurred, a 20-gauge needle was used intraoperatively and postoperatively to relieve pneumoperitoneum.

A jejunal nutrition tube with the tip near the duodenal wound and a gastric tube were placed for drainage and detection of any postoperative hemorrhage. After the procedure, all patients were fasted and treated with a proton-pump inhibitor and prophylactic antibiotics. Oral intake was gradually resumed according to wound recovery.

Postoperative specimen management and pathological evaluation

After the operation, the resected specimens were observed and measured, and their size, shape, and envelope integrity were recorded. Then the specimens were immersed in 4% formaldehyde solution and fixed. Hematoxylin and eosin staining and immunohistochemistry were performed routinely. A diagnosis of GIST was confirmed if microscopic spindle cell proliferation was seen in the fasciculate, with staggered arrangement and positivity for CD117 or DOG-1 and CD34 (Figure 1L-R). The risk of recurrence after resection of GISTs was assessed according to the National Institutes of Health risk stratification system (2008 modified)[14].

Definition of terms and outcome assessment

Complete resection was considered if the lesion was resected en bloc with no obvious residual tumor at the resection site and with tumor-free margins according to histopathological examination[15]. Complications included intraoperative perforation, delayed perforation, intraoperative bleeding, delayed bleeding, and perioperative infection. Intraoperative perforation was considered if an extra-duodenal structure was visualized, retroperitoneal pneumatosis occurred, or free gas was detected by CT examination immediately after resection of the lesion[16]. Delayed perforation was considered if the patient experienced sudden abdominal pain after the procedure with a duodenal defect found under endoscopy or surgery. Intraoperative bleeding was regarded as a complication if one of the following criteria was met: (1) During the procedure, bleeding affected the visual field and could not be managed by endoscopic methods; (2) There was a significant reduction in hemoglobin (> 2 mg/dL); or (3) Blood transfusion was required[17]. Delayed bleeding was defined as hemorrhage from a post-procedure ulcer [18]. Local recurrence was defined as the detection of a lesion located on or adjacent to the scar of the previous endoscopic resection, which was then pathologically confirmed by biopsy[15].

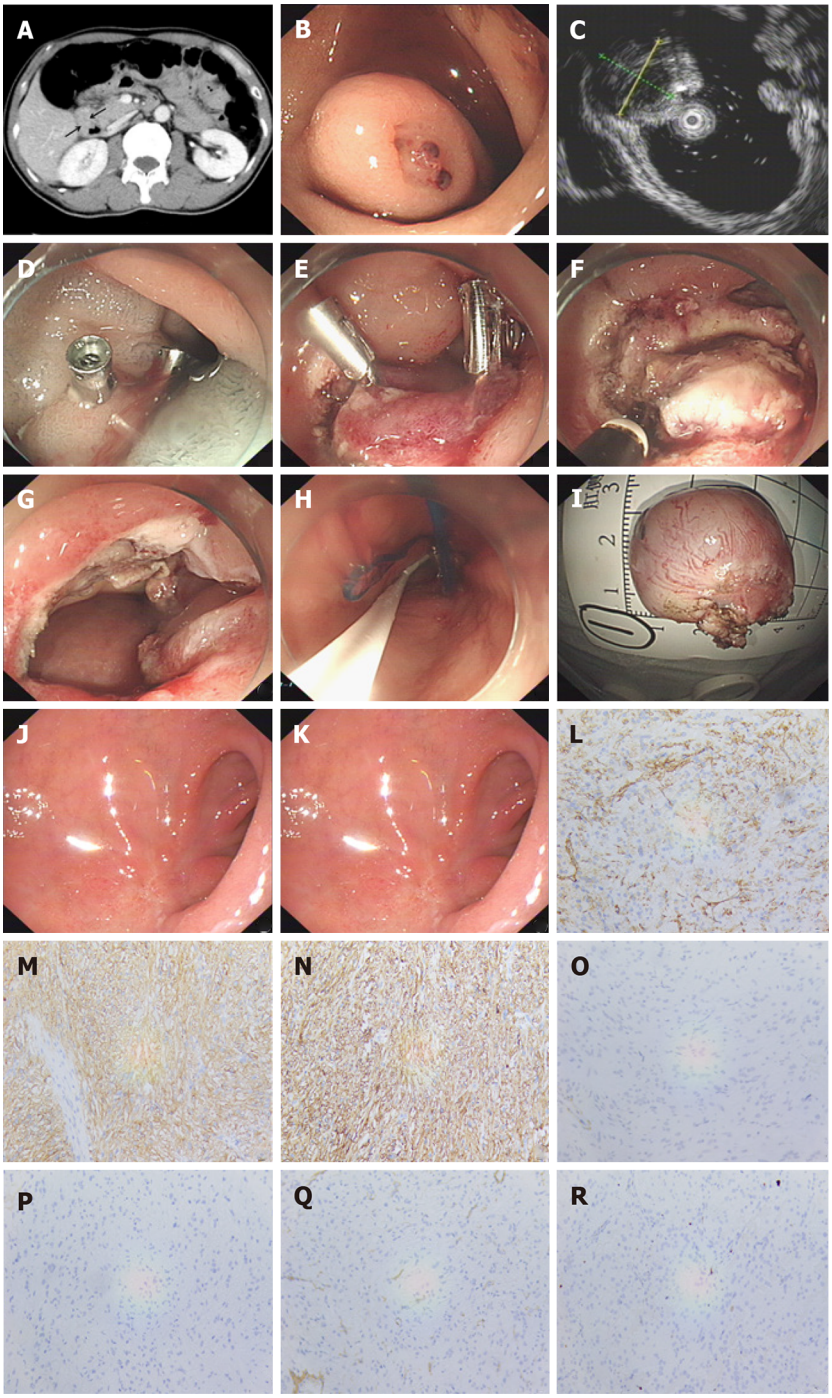

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Figure 1 Endoscopic full-thickness resection for duodenal gastrointestinal stromal tumors in the descending junction of the duodenal bulb. A: Computed tomography revealed a tumor of approximately 3 cm in diameter, with enhancement in the arterial phase; B: A tumor located in the descending junction of the duodenal bulb with ulcer and exposed blood vessels on the surface. Titanium clips were used to stop the bleeding; C: The endoscopic ultrasonography showed that the lesion was a hypoechoic structure originating from the muscularis propria layer, with uniform echo and a clear boundary; D: Submucosal injection after making several marking dots around the lesion; E: A circumferential incision was made outside the border; F: The submucosa and muscularis propria around the lesion were circumferentially dissected; G: The duodenal defect after tumor resection; H: The wound was occluded with several titanium clips + an endoloop + an over-the-scope clip. A jejunal nutrition tube was placed near the wound for drainage; I: The resected tumor with the intact capsule; J: The wound healed well at 3 mo after the procedure; K: Hematoxylin and eosin staining (original magnification × 40); L: Immunohistochemistry showed that the tumor was positive for CD34; M: Immunohistochemistry showed that the tumor was positive for CD117; N: Immunohistochemistry showed that the tumor was positive for Dog-1; O: Immunohistochemistry showed that the tumor was negative for desmin; P: Immunohistochemistry showed that the tumor was negative for S-100; Q: Immunohistochemistry showed that the tumor was negative for SMA; and R: Immunohistochemistry showed that Ki67 was about 2%.

Follow-up

Every patient underwent EUS at 3 mo after the operation to evaluate wound healing and check for residual lesions. The second surveillance endoscopy procedure was performed at 6 mo. Subsequently,

gastroscopy and/or EUS was performed to detect tumor recurrence, and CT and/or abdominal ultrasound was used every 12 mo if any distant metastasis was detected; this was continued indefinitely.

Statistical analysis

Data were presented as the mean, median, number of cases, and percentage. All statistical analyses were performed using the SPSS software program (version 20.0; SPSS Inc, Armonk, NY, United States).

RESULTS

Clinical characteristics

The patient and tumor characteristics are summarized in Table 1. A total of 11 patients (male, n = 9; female, n = 2) with duodenal GISTs underwent endoscopic resection at our center. The median age was 55 years (range: 33–74 years). Eight patients (72.7%) were symptomatic at presentation, with melena in 6 patients (54.5%), abdominal pain in 1 patient (9.1%), and abdominal distension in 1 patient (9.1%). Three tumors (27.3%) were detected incidentally during endoscopy for other reasons. All patients were negative for immunologic series and tumor markers (AFP, CEA, CA199, and CA125). Patients with gastrointestinal hemorrhaging showed fecal occult blood positivity and had anemia, with a minimum hemoglobin level of 36 g/L. All patients showed duodenal mass on abdominal CT before operation, which was enhanced after enhancement.

The lesions were single in all 11 patients. The lesion was detected in the duodenal bulb in 2 cases (18.2%), in the descending junction of the duodenal bulb in 4 cases (36.4%), and in the descending part in 5 cases (45.4%). All lesions originated from the MP layer with intraluminal growth in 6 cases (54.5 %), partially extraluminal growth in 2 cases (18.2%), and mainly extraluminal growth in 3 cases (27.3%). EUS revealed hypoechoic structures in 10 cases (90.9%) and a mixed echoic structure in 1 case (9.1%). The median maximal diameter of these lesions was 3.0 cm (range: 1.5-5.0 cm). Immunohistochemistry of all lesions showed that CD34, CD117, and Dog-1 were positive, and Desmin and S-100 were negative. Nine cases (81.8%) were SMA positive. Four cases (36.4%) were Ki-67 < 1%, 3 cases (27.3%) were Ki-67 1%+, 3 cases (27.3%) were Ki-67 2%+, and 1 case (9.1%) was Ki-67 3%+.

Treatment outcomes

Complete resection was successful in 100% of cases. Four patients (36.4%) were classified as very low risk, and 7 patients (63.6%) were classified as low risk. Among the 11 patients, a positive resection margin was suspected in 3 cases (27.3%) (tumor tissue was found at the electrocautery margin); all cases were pathologically low risk. The remaining 8 cases (72.7%) had negative lateral and basal margins. All 11 patients recovered and were discharged.

Complications

Perforation was detected in all 11 patients during the operation. The duodenal wall defect was occluded with several titanium clips + an endoloop in 1 case (9.1%), an OTSC in 6 cases (54.5%), and an OTSC + several titanium clips + an endoloop in 4 cases (36.4%). Intraoperative perforation closure was successfully performed in 100% of cases. Delayed perforation was suspected in 1 patient (9.1%) (as described below).

All 11 patients had bleeding during the procedure and were treated successfully using argon plasma coagulation and a hot biopsy forceps. A little coffee-colored liquid was drained from the gastrointestinal decompression tube in 1 case (9.1%) on the 1st d after the procedure, which improved after strengthening the acid inhibition and using somatostatin.

Six patients (54.5%) developed postoperative abdominal infection, and their anti-infection treatment was strengthened. Among them, 1 patient developed severe abdominal pain and septic shock on the day after endoscopic resection of a 3.0 cm × 2.5 cm tumor in the descending junction of the duodenal bulb. Emergency surgical exploratory laparotomy was performed immediately for suspected delayed perforation. During the operation, obvious edema was observed on the wound, but no obvious perforation was detected. This patient received peritoneal lavage and distal subtotal gastrectomy with resection of the duodenal bulb. Another patient developed a right iliac fossa abscess, which improved after puncture and drainage. One patient (9.1%) suffered malignant arrhythmia 5 d after the procedure and was transferred to the intensive care unit. All 11 patients recovered and were discharged. The mean time to the recovery of food intake after the operation was 8.1 d (range: 4-14 d). The mean postoperative hospital stay was 15.3 d (range: 8-26 d).

Follow-up

The wound healed well in all patients, and no recurrence or distant metastasis was detected during the follow-up period (median: 36 mo; range: 14-80 mo). Duodenal stenosis occurred in 1 patient (9.1%) whose previous tumor was in the descending junction of the duodenal bulb, and the wound was closed by an OTSC. The OTSC was found to block the lumen, and the endoscope could not pass through at 3

Table 1 Clinical characteristics of 11 duodenal gastrointestinal stromal tumors cases

Patient	Sex	Age, yr	Clinical presentation	Location	Size of maximum diameter, cm	Growth pattern	EUS appearance	Risk assessment	Specimen margin	Postoperative hospital stay, d	Follow-up, mo
1	M	57	Melena	Duodenal bulb	2.2	Mainly extraluminal growth	MP, hypoecho, uniform echo	Low risk	Negative	9	14
2	M	56	No symptoms	Descending junction of duodenal bulb	2.0	Intraluminal growth	MP, hypoecho, uniform echo	Very low risk	Negative	15	19
3	M	68	No symptoms	Descending duodenum	3.0	Partially extraluminal growth	MP, hypoecho, uniform echo	Low risk	Negative	11	22
4	M	63	Melena	Descending duodenum	5.0	Mainly extraluminal growth	MP, hypoecho, uniform echo	Low risk	Suspiciously positive	16	30
5	M	52	Melena	Descending duodenum	1.5	Intraluminal growth	MP, mixed echo, uneven echo	Very low risk	Negative	8	33
6	M	53	Melena	Descending junction of duodenal bulb	3.5	Mainly extraluminal growth	MP, hypoecho, uniform echo	Low risk	Suspiciously positive	15	36
7	M	54	Melena	Descending duodenum	4	Intraluminal growth	MP, hypoecho, uniform echo	Low risk	Suspiciously positive	24	43
8	M	74	Melena	Descending junction of duodenal bulb	3.0	Intraluminal growth	MP, hypoecho, uniform echo	Low risk	Negative	26	50
9	F	33	Abdominal pain	Descending duodenum	3.0	Intraluminal growth	MP, hypoecho, uniform echo	Low risk	Negative	14	51
10	F	42	No symptoms	Descending junction of duodenal bulb	1.5	Intraluminal growth	MP, hypoecho, uniform echo	Very low risk	Negative	13	75
11	M	55	Abdominal distension	Duodenal bulb	2.0	Intraluminal growth	MP, hypoecho, uniform echo	Very low risk	Negative	12	80

EUS: Endoscopic ultrasonography; F: Female; M: Male; MP: Muscularis propria.

mo after the procedure. The patient was followed up, as he had no symptoms of obstruction. During endoscopic surveillance at 12 mo after the procedure, the OTSC detached spontaneously, and the lumen stenosis improved.

DISCUSSION

Endoscopic resection of duodenal lesions, especially subepithelial lesions, is still considered a challenging procedure due to the unique anatomical and endoscopic features of the duodenum. The duodenal lumen is rather narrow, and the initial part (bulbar to descending part) is an anti-c-shaped loop, which makes endoscopic operations difficult. The mucosa is difficult to lift after the injection due to the abundant Brunner's gland and blood vessels in the submucosa of the duodenum, which also increases the difficulty of treatment. Traditionally, the duodenum has been regarded as a forbidden zone for endoscopic excision of duodenal subepithelial lesions, especially for endoscopic full-thickness resection. The rapid de-velopment of endoscopic techniques and endoscopic devices makes endoscopic resection for duodenal GISTs another acceptable alternative to minimize morbidity.

For localized GISTs, complete excision is the standard treatment. R0 resection is the goal in any case. A post hoc observational study showed that among patients with GISTs, when tumor rupture was excluded, there was no significant difference in overall survival of patients who received R0 and R1 resection[19]. Some studies also indicated that the recurrence rate of patients who received R1 resection did not differ from that of patients who received R0 resection[20,21]. Thus, if R0 resection is difficult to achieve, R1 resection (microscopically positive margins) may also be performed for low-risk GISTs in unfavorable locations[7]. If R1 resection was already performed, routine re-excision is not recommended [7], and the microscopic margin status should not be used to dictate adjuvant medical therapy decisions [19]. In our study, there were 3 cases in which microscopic involvement of the resection margins was suspected; all were low risk. No recurrence or distant metastasis was found during follow-up (30 mo, 36 mo, and 43 mo) without re-excision or adjuvant medical therapy.

Tumor rupture is an important adverse prognostic factor for the recurrence of GIST. It is defined by tumor spillage or fracture in the abdominal cavity, piecemeal resection, incisional biopsy, gastric or intestinal perforation to the abdominal cavity, blood-stained ascites at laparotomy, or transperitoneal microscopic infiltration of an adjacent organ[7]. In our study, the maximal diameter of all tumors was ≤ 5 cm and were resected en bloc. When the tumor size is > 5 cm in diameter, it is very difficult to resect it completely and take it out as a whole through the cardia, esophagus, and pharynx. Thus, for tumors larger than 5 cm, especially in intermediate- and high-risk cases, conventional surgery or laparoscopic and endoscopic cooperative surgery may be more appropriate.

In comparison to other parts of the digestive tract, the muscular layer of the duodenum is much thinner, and intraoperative perforation is prone to occur during endoscopic operations. In addition, digestive fluids, such as bile and pancreatic juice, can corrode the wound, and delayed perforation may subsequently occur. Injury to the duodenal muscularis and serosa should be avoided as far as possible in the case of perforation. However, when the lesion is closely associated with the MP or serosal layer of the duodenum, perforation is almost inevitable. Most duodenal GISTs originate from the MP, and the strategy "active perforation" is often adopted, resulting in a well-defined edge and mild edema. In some studies, perforation that could be closed by endoscopic methods during the endoscopic operation was not regarded as a complication[22,23].

With the development of endoscopic suture technology and the invention of OTSC, the OverStitch endoscopic suturing (ES) device and other suture devices, the success rate of wound suturing has been greatly improved. An OTSC has the following advantages: (1) It has great holding strength[24,25]; thus, it can grasp more tissue and clamp the entire wall of the lumen; (2) It is a bear trap-like, large clip with a wingspan of 12 mm, which can close full-thickness perforations of up to 3 cm in diameter[26]; and (3) The gap between the teeth of an OTSC allows blood to pass through to avoid tissue necrosis.

A systematic review showed that the rate of successful closure of the perforation by OTSC closure was 85.3%[27]. In our previous study, OTSC successfully closed the perforation after endoscopic resection of duodenal subepithelial lesions in 100% of cases, without delayed perforation[28]. The OverStitch ES device is designed for tissue approximation and allows the creation of either interrupted or continuous running stitches. Thus, it can reliably close perforations[29]. In a study by Chung *et al* [30], the OverStitch ES device was applied in 7 cases after endoscopic mucosal resection of large duodenal adenomas, and all ES sessions were technically successful.

In addition, purse-string suture technique, which is also widely used in iatrogenic digestive tract perforation, shows a high rate of successful sealing. Our previous study suggested that the closure rate of purse-string suture in endoscopic treatment of duodenal subcutaneous lesions was 100% (including 5 cases of perforation)[31]. In this study, duodenal wall defects were all successfully closed using OTSC, titanium, or purse-string suture according to the size of wound and wall defect. We placed two tubes, one with the tip in the gastric cavity to attract gas and gastric juice, and the other with the tip next to the duodenal wound to attract pancreatic juice and bile. Lessening tension of the wound and reducing the corrosion of digestive juice to the wound could effectively decrease the occurrence of delayed perforation.

Another serious complication of endoscopic resection of duodenal GISTs is perioperative infection followed by perforation. In this study, 6 patients had postoperative abdominal infection, including 1 who developed septic shock and another who developed an abscess in the right iliac fossa. During the procedure, suction should be carried out in a timely manner in order to prevent excessive blood, intestinal contents, and digestive juices flowing into the retroperitoneum. The wound should be closed as soon as possible after the lesion is removed. When a large volume of liquid has overflowed into the retroperitoneum, timely flushing and drainage can also reduce the incidence of infection. Besides, if the lesion is really difficult to remove endoscopically, timely conversion to surgery or laparoscopic-assisted resection may be a wiser option.

In addition, it should be noted that the duodenal lumen is relatively narrow, especially in the descending junction of the duodenal bulb, and postoperative stricture may occur. In this study, 1 patient developed stricture after the wound was closed with an OTSC. When treating the wound, especially when placing the OTSC, attention should be paid to avoid grasping too much tissue in the case of duodenal lumen stenosis.

The present study was associated with some limitations. First, this was a single center retrospective study with a relatively small sample size, and a selection bias may have been present. Second, there was a lack of randomized and controlled samples. Third, the follow-up period of some cases was relatively short.

CONCLUSION

Endoscopic resection for duodenal GISTs appears to be effective and safe in selected cases. The procedure should be performed by a senior endoscopist who has rich experience in the management of complications of endoscopic operations for duodenal lesions. If the lesion is difficult to remove endoscopically or there are severe complications that cannot be managed by conservative treatment or an endoscopic method, surgery should be performed in a timely manner.

ARTICLE HIGHLIGHTS

Research background

Currently, endoscopic resection of duodenal gastrointestinal stromal tumors (GISTs) is a challenging procedure with a high risk of complications.

Research motivation

Traditional surgical treatment methods for duodenal GISTs are traumatic and prone to serious complications. Endoscopic resection of duodenal GISTs is an alternative. However, there are few reports on endoscopic treatment for duodenal GISTs.

Research objectives

We aimed to evaluate the effectiveness and safety of endoscopic resection for duodenal GISTs.

Research methods

This was a retrospective study. We collected data of 11 consecutive patients with duodenal GISTs who were treated with endoscopic resection and analyzed the rate of complete resection, bleeding, perforation, postoperative infection, recurrence, and distant metastasis.

Research results

All lesions were completely resected, while three cases (27.3%) had suspected positive margins. No local recurrence or distant metastasis were detected during the follow-up period in any of the patients.

Research conclusions

Endoscopic resection for duodenal GISTs appears to be an effective and safe treatment by an experienced endoscopist.

Research perspectives

We need to expand the sample size to further confirm the effectiveness and safety of endoscopic resection of duodenal GISTs. In addition, the long-term outcome should be observed by extending the follow-up time.

FOOTNOTES

Author contributions: Wang ZZ, Mao XL, Yan XD, and Yang HD participated in the clinical treatment; Wang ZZ, Fu XY, and Cai Y wrote the original draft; Li SW undertook validation, writing, reviewing, and editing; All authors contributed to the article and approved the submitted version.

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ORIGINAL ARTICLE

Retrospective Study

Impact of looping on premalignant polyp detection during colonoscopy

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Abstract

BACKGROUND

The presence of premalignant polyps on colonoscopy is an indicator of metachronous colorectal cancer. Looping during colonoscopy is associated with old age, female sex, and colonoscopy insertion time. However, the clinical significance of looping is not fully understood. We aimed to clarify the effect of looping on colorectal premalignant polyp detection.

AIM

To assess the effects of looping on premalignant polyp detection using logistic regression analyses.

METHODS

We retrospectively investigated patients who underwent colonoscopy at Toyoshima Endoscopy Clinic between May, 2017 and October, 2020. From the clinic's endoscopy database, we extracted data on patient age, sex, endoscopist-assessed looping, colonoscopy duration, endoscopist experience, detection rate, and number of premalignant polyps.

RESULTS

We assessed 12259 patients (mean age, 53.6 years; men, 50.7%). Looping occurred in 54.3% of the patients. Mild and severe looping were noted in 4399 and 2253 patients, respectively. The detection rates of adenomas, advanced adenomas, high-risk adenomas, clinically significant serrated polyps (CSSPs), and sessile serrated lesions (SSLs) were 44.7%, 2.0%, 9.9%, 8.9% and 3.5%, respectively. The mean numbers of adenomas and SSLs were 0.82 and 0.04, respectively. The detection rates of adenomas, high-risk adenomas, and CSSPs increased with looping severity (all $P < 0.001$). The number of adenomas increased with looping severity ($P < 0.001$). Multivariate analyses found that detection of adenomas, high-risk adenomas, and CSSPs was associated with severe looping ($P < 0.001$, $P < 0.001$, and $P = 0.007$, respectively) regardless of age, sex, time required for colonoscope insertion and withdrawal, and endoscopist experience.

CONCLUSION

Looping severity was independently associated with high detection rates of premalignant polyps. Therefore, looping may predict the risk of metachronous colorectal cancer. Endoscopists should carefully examine the colorectum of patients with looping.

Key Words: Looping; Colorectal polyp; Colonoscopy; Adenoma; Serrated polyp; Colorectal neoplasm

Core Tip: This study aimed to clarify the effect of colonic looping on colorectal premalignant polyp detection during colonoscopy. We retrospectively investigated 12259 patients who underwent colonoscopies. Looping occurred in 54.3% (35.9% and 18.4% with mild and severe looping, respectively) of the cases. The detection rates of adenomas (44.7%), high-risk adenomas (9.9%), and clinically significant serrated polyps (CSSPs) (8.9%) increased with the looping severity. The number of adenomas per colonoscopy (0.82) increased with the looping severity. Multivariate analyses found that detection of adenomas, high-risk adenomas, and CSSPs was associated with severe looping regardless of age, sex, time required for colonoscope insertion and withdrawal, and endoscopist experience.

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INTRODUCTION

Colorectal cancer mainly occurs because of adenomas or serrated polyps[1-3]. Colonoscopy is the gold standard for cancer screening and detection of premalignant polyps. The prevalence of metachronous colorectal cancer is high in patients with adenomas, especially high-risk adenomas, removed during colonoscopy[4]. Similarly, individuals with colonoscopically resected clinically significant serrated polyps (CSSPs) have a long-term risk of colorectal cancer[5-7]. Thus, the detection of adenomas and CSSPs on colonoscopy is a surrogate marker for the risk of metachronous colorectal cancer. Factors related to premalignant polyp detection include patient characteristics, such as age and sex[8,9], endoscopic procedure-related factors, such as cecal intubation time[10] and withdrawal time[11-14], and endoscopist experience[8].

Colonic looping is a common obstacle during routine colonoscopy[15,16]. Looping is associated with a redundant colon, older age, female sex, and cecal intubation time[17-20]. However, the clinical significance of looping is poorly understood. Therefore, this study aimed to clarify the effect of looping on colorectal premalignant polyp detection by using multivariate analysis to control for potential confounding factors.

MATERIALS AND METHODS

Study design and overview

This retrospective study was conducted at a single institute, Toyoshima Endoscopy Clinic, a representative outpatient endoscopy-specialized clinic located in an urban area of Japan. Toyoshima

Endoscopy Clinic performs 10000 endoscopies annually. The study design was described in a protocol prepared at Toyoshima Endoscopy Clinic and approved by the Certified Institutional Review Board of Yoyogi Mental Clinic on July 16, 2021 (Approval no. RKK227). We published this study's protocol on our institute's website (www.ichou.com). Thus, patients could opt out of the study if desired. All the authors approved the final manuscript. No funding was received for this study.

Patients

Patients who underwent colonoscopy at Toyoshima Endoscopy Clinic between May, 2017 and October, 2020 were enrolled in this study. The indications for colonoscopy included the examination of symptoms and abnormal findings, screening, and surveillance for colorectal diseases. Patients undergoing treatment, such as polypectomy and hemostasis, those with poor bowel preparation[21,22], and those with a history of colorectal surgery were excluded. Cases of colonoscopies with incomplete cecal intubation, withdrawal time of < 6 min[11], and those performed with an ultrathin colonoscope were also excluded[23].

Definition of looping

Common colonic looping patterns observed during colonoscopy have been described previously. Loops occur in the transverse and sigmoid colons, and sigmoid loops include alpha and N shapes[19,24]. When forming a loop, there is no one-to-one relationship between the transmission of the colonoscope shaft movement and colonoscope tip motion. In the case of looping, further insertion of the scope results in a larger loop size without de-looping the scope[24,25].

Cecal insertion without loop formation was defined as the absence of looping. Cecal insertion that required straightening of the colonic loop once was defined as mild looping. Cecal insertion that required straightening of the colonic loop two or more times was defined as severe looping.

Colonoscopy

Small and gentle shaking and jiggling of the colonoscope shaft were performed. Right-turn shortening maneuvers for straightening the shaft were used for colonoscope insertion. Water-assisted, carbon dioxide-assisted, and cap-assisted chromoendoscopies with sedation were performed[26]. Position changes and rectal retroflexion were performed[8,27]. When looping was formed, we usually controlled the colonoscope by changing the patient's position to supine or right lateral, and manual abdominal compression was performed by the assistant[15].

Thirty endoscopists with various levels of experience performed the colonoscopies[28,29]. This study defined experienced endoscopists as those with > 15 years of experience in performing endoscopy. We used a combination of the Elite system and CF-HQ290ZI, CF-HQ290I, or PCF-H290ZI colonoscopes (Olympus Corporation, Tokyo, Japan). Poor bowel preparation was defined as at least one colon segment that could not be examined because of the presence of remnant solid stool[9,16,27].

Colorectal polyps

All polyps suspected to be cancerous, adenomatous, or CSSP were removed or biopsied. All polyps were histologically diagnosed by an experienced gastrointestinal pathologist using the resected specimens and biopsy samples. Advanced adenomas included adenomas ≥ 10 mm in size, villous adenomas, and adenomas with high-grade dysplasia. A high-risk adenoma was defined as the presence of advanced adenoma and/or three or more adenomas. CSSPs comprise all sessile serrated lesions (SSLs), all traditional serrated adenomas, hyperplastic polyps of size ≥ 10 mm anywhere in the colorectum, and hyperplastic polyps of size ≥ 5 mm located between the cecum and descending colon[30-33].

Outcomes

We extracted data from the endoscopy database of Toyoshima Endoscopy Clinic, including patient age, sex, endoscopist-assessed looping, colonoscope insertion time, withdrawal time, endoscopists, detection rates of adenomas, advanced adenomas, high-risk adenomas, CSSPs, and SSLs, and numbers of adenomas and SSLs. Withdrawal time was defined as the time required to examine the colorectal mucosa and remove the polyps. The polyp detection rate was defined as the rate of colonoscopies that detected at least one polyp.

Statistical analysis

The significance of any orderly increase or decrease along the three stratifications (*i.e.*, no, mild, and severe looping) was assessed using Cochran-Armitage trend test or Jonckheere-Terpstra trend test for categorical and continuous variables, respectively. Because of the significant association between looping severity and polyp detection in the trend test, the effect of subject characteristics on polyp detection was analyzed using a multivariate analysis. Furthermore, a subgroup analysis, limited to experienced endoscopists, was performed. Multivariate analysis was performed using a binomial logistic regression model, with no, mild, and severe looping scores of 0, 1, and 2, respectively. Statistical significance was defined as a P-value < 0.05. The calculations were performed using Bell Curve for Excel version 3.22 (Social Survey Research Information Co., Ltd., Tokyo, Japan) and R version 4.1.2 (R Core

Team 2021, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients

During the study period, colonoscopies were performed on 13315 patients. We excluded 236 patients undergoing treatment, such as polypectomy and hemostasis, 77 with poor bowel preparation, 217 with previous colorectal surgery, 20 with incomplete cecal insertion (including 8 with stenosis caused by colorectal tumor and 6 with colonic looping), 22 with withdrawal time < 6 min, and 484 who were examined using an ultrathin colonoscope. Ultimately, 12259 patients were enrolled in this study. A patient flowchart is shown in Figure 1.

The mean patient age was 53.6 years. Men accounted for 50.7% of the participants. Looping occurred in 54.3% of the patients. There were 4399 and 2253 patients with mild and severe looping, respectively. The mean insertion and withdrawal times were 4.6 and 13.9 min, respectively. Experienced endoscopists performed 70.4% of the colonoscopies. The polyp detection rates for adenomas, advanced adenomas, high-risk adenomas, CSSPs, and SSLs were 44.7%, 2.0%, 9.9%, 8.9%, and 3.5%, respectively. The mean number of adenomas and SSLs was 0.82 and 0.04, respectively (Table 1).

Subject characteristics based on looping

Patients with severe looping tended to be older and more likely to be female (both $P < 0.001$). Cecal insertion and withdrawal times tended to be longer in severe looping (both $P < 0.001$). Experienced endoscopists performed cases with severe looping more often. The polyp detection rates of adenomas ($P < 0.001$), advanced adenomas, high-risk adenomas ($P < 0.001$), CSSPs ($P < 0.001$), and SSLs tended to increase with looping severity. However, the tendency of advanced adenoma and SSL detection rates were not statistically significant ($P = 0.166$ and $P = 0.064$, respectively). The number of adenomas increased with looping severity ($P < 0.001$, Table 2).

Multivariate analysis of effect on polyp detection

We investigated the effect of subject characteristics on the detection of adenomas, high-risk adenomas, and CSSPs using multivariate analyses. The detection of adenomas and high-risk adenomas was independently associated with severe looping (both $P < 0.001$), old age, male sex, short insertion time, long withdrawal time, and endoscopist experience. CSSP detection was independently associated with severe looping ($P = 0.007$), female sex, short insertion time, long withdrawal time, and endoscopist experience (Table 3).

Subgroup analysis limited to experienced endoscopists

We performed a subgroup analysis that was limited to experienced endoscopists. Multivariate analyses showed similar results to the all-case analyses, that is, severe looping was independently associated with high detection rates of adenomas, high-risk adenomas, and CSSPs ($P < 0.001$, $P < 0.001$, and $P = 0.008$, respectively; Table 4).

DISCUSSION

In this study, we found that the severity of looping during colonoscopy was positively associated with high detection rates of adenomas, high-risk adenomas, and CSSPs, independent of other confounding factors, such as patient age, sex, colonoscope insertion and withdrawal times, and endoscopist experience. To the best of our knowledge, this is the first study to demonstrate a relationship between looping and polyp detection. Adenomas, high-risk adenomas, and CSSPs are precancerous lesions[2]. Recent studies have also shown that adenoma, high-risk adenoma, and CSSP detection rates are associated with a high risk of metachronous colorectal cancer[4,6]. Therefore, looping may predict a high frequency of metachronous colorectal cancer; however, further analysis is needed. Colonoscopists should carefully examine the colorectal region of patients with looping considering the high premalignant polyp detection rate.

Magnetic endoscopic imaging, computed tomographic colonoscopy, and autopsy revealed that looping was more common in older adults and women. Loop formation is also associated with prolonged cecal insertion time[17-20]. In our study, looping severity was associated with older age, female sex, and longer insertion time. Our results were consistent with those of previous studies. Looping during colonoscopy mainly occurs in the intraperitoneal segments of the colon, such as the transverse and sigmoid colon[15,17,19,20,34,35]. Barium enema and computed tomographic colonoscopy revealed that older adults and women had longer colons and larger colonic surface areas than younger adults and men, respectively. Differences in the total length and surface area are predominantly due to differences in the transverse colon[36-38]. The increased length and surface area of the

Table 1 Characteristics of the study subjects

Characteristics	
n	12259
Age, mean (SD), yr	53.6 (12.2)
Male sex, %	50.7
Looping, none/mild/severe, *n*	5532/4399/2253
Insertion time, mean (SD), min	4.57 (2.66)
Withdrawal time, mean (SD), min	13.87 (4.19)
Experienced endoscopist, %	70.4
Polyp detection	
Adenoma DR, %	44.7
Advanced adenoma DR, %	2.0
High-risk adenoma DR, %	9.9
CSSP DR, %	8.9
SSL DR, %	3.5
Number of adenomas, mean (SD), *n*	0.82 (1.25)
Number of SSLs, mean (SD), *n*	0.04 (0.24)

SD: Standard deviation; DR: Detection rate; CSSP: Clinically significant serrated polyp; SSL: Sessile serrated lesion.

Table 2 Subject characteristics based on looping severity

	No looping	Mild looping	Severe looping	*P* value
n	5532	4399	2253	
Age, mean (SD), yr	51.5 (11.5)	54.2 (12.2)	56.7 (13.0)	< 0.001
Male sex, %	62.8	44.6	33.4	< 0.001
Insertion time, mean (SD), min	3.53 (1.89)	4.95 (2.41)	6.38 (3.44)	< 0.001
Withdrawal time, mean (SD), min	13.70 (4.30)	14.17 (4.29)	13.74 (3.66)	< 0.001[1]
Experienced endoscopist, %	61.1	73.7	87.6	< 0.001
Polyp detection				
Adenoma DR, %	42.2	45.0	50.2	< 0.001
Advanced adenoma DR, %	1.8	2.1	2.3	0.166
High-risk adenoma DR, %	8.4	9.8	13.5	< 0.001
CSSP DR, %	7.8	9.5	10.3	< 0.001
SSL DR, %	3.2	3.7	3.9	0.064
Number of adenomas, mean (SD), *n*	0.74 (1.16)	0.81 (1.25)	1.03 (1.44)	< 0.001
Number of SSLs, mean (SD), *n*	0.04 (0.22)	0.05 (0.26)	0.05 (0.26)	0.553

[1]There were 22065005 and 19833488 combinations of increasing and decreasing trends, respectively.

P values were calculated using Cochran–Armitage trend test and Jonckheere-Terpstra test for categorical and continuous variables, respectively. SD: Standard deviation; DR: Detection rate; CSSP: Clinically significant serrated polyp; SSL: Sessile serrated lesion.

colon may contribute to the formation of loops and high frequency of premalignant polyps.

Colonic redundancy is a major cause of looping during colonoscopy[39]. Colonic elongation and tortuosity appear to be related to redundancy of the colon, such as in the transverse and sigmoid colon [40,41]. Older adults and women often present with colonic redundancy and looping[41]. Raahave *et al* [42] reported that colonic transit time is associated with redundant colonic loops. Constipation increases

Table 3 Multivariate analysis of the effect on polyp detections

	Odds ratio	95% confidence interval	DOF	*P* value
Adenoma				
Looping[1]	1.13	1.06-1.20	1	< 0.001
Age	1.05	1.04-1.05	1	< 0.001
Male sex	1.39	1.28-1.50	1	< 0.001
Insertion time	0.94	0.92-0.96	1	< 0.001
Withdrawal time	1.14	1.13-1.15	1	< 0.001
Endoscopist experience	1.68	1.53-1.85	1	< 0.001
High-risk adenoma				
Looping[1]	1.25	1.13-1.38	1	< 0.001
Age	1.05	1.05-1.06	1	< 0.001
Male sex	1.527	1.33-1.74	1	< 0.001
Insertion time	0.90	0.87-0.93	1	< 0.001
Withdrawal time	1.20	1.18-1.21	1	< 0.001
Endoscopist experience	3.91	3.17-4.82	1	< 0.001
Clinically significant serrated polyp				
Looping[1]	1.14	1.04-1.26	1	0.007
Age	1.00	0.99-1.01	1	0.999
Male sex	0.60	0.52-0.68	1	< 0.001
Insertion time	0.92	0.88-0.95	1	< 0.001
Withdrawal time	1.16	1.14-1.17	1	< 0.001
Endoscopist experience	2.04	1.71-2.43	1	< 0.001

[1]No, mild, and severe looping were scored 0, 1, and 2, respectively.
P value was calculated using binomial logistic regression model. DOF: Degree of freedom.

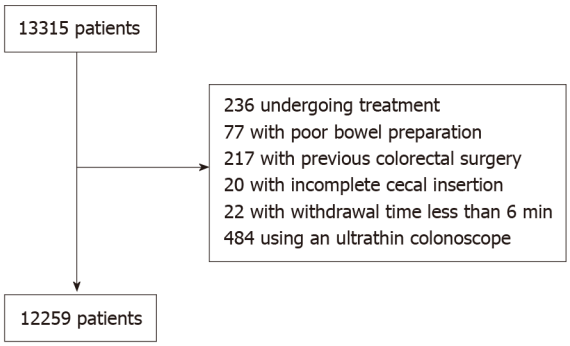

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Figure 1 Patient flowchart.

the risk of colorectal cancer[43]. This causes prolonged contact between the colonic mucosa and carcinogens in the stool.

Our study showed that adenoma detection was associated with old age, male sex, short insertion time, long withdrawal time, and endoscopist experience. These results are consistent with those of previous studies[8,10-12]. Female sex and longer withdrawal time, but not older age, were associated with CSSPs in our study. These findings are also concordant with those of previous studies[44-46]. The consistency of these results strengthens the credibility of this study.

Table 4 Multivariate analysis of the effect on polyp detections in the sub-analysis of experienced endoscopists

	Odds ratio	95% confidence interval	DOF	*P* value
Adenoma				
Looping[1]	1.14	1.07-1.23	1	< 0.001
Age	1.05	1.05-1.05	1	< 0.001
Male sex	1.42	1.29-1.56	1	< 0.001
Insertion time	0.93	0.91-0.95	1	< 0.001
Withdrawal time	1.13	1.11-1.14	1	< 0.001
High-risk adenoma				
Looping[1]	1.27	1.14-1.41	1	< 0.001
Age	1.05	1.05-1.06	1	< 0.001
Male sex	1.56	1.35-1.81	1	< 0.001
Insertion time	0.89	0.85-0.92	1	< 0.001
Withdrawal time	1.18	1.16-1.20	1	< 0.001
Clinically significant serrated polyp				
Looping[1]	1.15	1.04-1.28	1	0.008
Age	1.00	1.00-1.01	1	0.627
Male sex	0.66	0.57-0.77	1	< 0.001
Insertion time	0.92	0.89-0.96	1	< 0.001
Withdrawal time	1.13	1.11-1.15	1	< 0.001

[1]No, mild, and severe looping were scored 0, 1, and 2, respectively.
P value was calculated using binomial logistic regression model. DOF: Degree of freedom.

Limitations

This study had several limitations. First, this study was retrospectively conducted at a single institution; however, medical data were well-controlled. Second, although patients' body mass index, family history of colorectal cancer, and gynecological surgery are associated with the presence of premalignant polyps and looping[25,47], they were not examined. Third, since mucosal exposure can affect adenoma detection rate[48], the shape of looping, de-looping method, and successful de-looping after cecal intubation should be evaluated, not only the degree of looping during insertion. However, our data do not contain this information. Further verification is required in the future.

CONCLUSION

In conclusion, the severity of looping during colonoscopy was strongly associated with high detection rates of premalignant polyps, such as adenomas, high-risk adenomas, and CSSPs. Therefore, looping may predict the risk of metachronous colorectal cancer; however, further investigation is needed. Endoscopists should be more careful when examining for colorectal polyps in patients with looping.

ARTICLE HIGHLIGHTS

Research background

Colonic looping is a common obstacle during routine colonoscopy.

Research motivation

Looping is associated with a redundant colon, older age, female sex, and cecal intubation time. However, the clinical significance of looping is not fully understood.

Research objectives
We aimed to clarify the effect of looping on colorectal premalignant polyp detection.

Research methods
We extracted data from the clinic's endoscopy database on patient age, sex, endoscopist-assessed looping, colonoscopy duration, endoscopist experience, and premalignant polyp detection. The effects of looping on premalignant polyp detection were assessed using logistic regression analyses.

Research results
The detection rates of adenomas, high-risk adenomas, and clinically significant serrated polyps (CSSPs) increased with the severity of looping (all $P < 0.001$). The number of adenomas increased with looping severity ($P < 0.001$). Multivariate analyses found that detection of adenoma, high-risk adenoma, and CSSP was associated with severe looping ($P < 0.001$, $P < 0.001$, and $P = 0.007$, respectively) regardless of age, sex, and the time required for colonoscope insertion and withdrawal, and endoscopist experience.

Research conclusions
Looping severity was independently associated with high detection rates of premalignant polyps.

Research perspectives
Looping may predict the risk of metachronous colorectal cancer; however, further investigation is needed.

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FOOTNOTES

Author contributions: Toyoshima O, Nishizawa T, Yoshida S and Fujishiro M designed the study; Toyoshima O, Nishizawa T, Yoshida S, Matsuno T, Arano T, and Kondo R contributed to the endoscopic diagnosis; Toyoshima O wrote the article; Toyoshima O and Yoshida S were responsible to the statistical analysis; Nishizawa T edited the article; Yoshida S, Matsuno T, Arano T, Kondo R, Kinoshita K, Yasumi Y, Tsuji Y, and Fujishiro M involved in the critical review; and all authors approved the final manuscript.

Institutional review board statement: This study was approved by the Certificated Review Board, Yoyogi Mental Clinic on July 16, 2021 (approval no. RKK227).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. For full disclosure, the details of the study are published on the home page of Toyoshima Endoscopy Clinic.

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Retrospective Study

Self-expanding metal stent placement and pathological alterations among obstructive colorectal cancer cases

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Abstract

BACKGROUND

Experimental studies suggest that self-expanding metal stents (SEMSs) enhance the aggressive behavior of obstructive colorectal cancer. The influence of SEMS placement on pathological alterations remains to be elucidated.

AIM

To determine whether SEMS placement is associated with molecular or pathological features of colorectal carcinoma tissues.

METHODS

Using a nonbiased molecular pathological epidemiology database of patients with obstructive colorectal cancers, we examined the association of SEMS placement with molecular or pathological features, including tumor size, histological type, American Joint Committee on Cancer (AJCC)-pTNM stage, and mutation statuses in colorectal cancer tissues compared with the use of transanal tubes. A multivariable logistic regression model was used to adjust for potential confounders.

RESULTS

SEMS placement was significantly associated with venous invasion ($P < 0.01$), but not with the other features examined, including tumor size, disease stage, mutation status, and lymphatic invasion. In both the univariable and mult-

ivariable models with adjustment for potential factors including tumor location, histological type, and AJCC-pT stage, SEMS placement was significantly associated with severe venous invasion ($P < 0.01$). For the outcome category of severe venous invasion, the multivariable odds ratio for SEMS placement relative to transanal tube placement was 19.4 (95% confidence interval: 5.24–96.2). No significant differences of disease-free survival and overall survival were observed between SEMS and transanal tube groups.

CONCLUSION

SEMS placement might be associated with severe venous invasion in colorectal cancer tissue, providing an impetus for further investigations on the pathological alterations by SEMSs in colorectal cancer development.

Key Words: Bridge to surgery; Colorectal carcinoma; Obstruction; Stent; Venous invasion

Core Tip: This study aimed to determine whether self-expanding metal stent (SEMS) placement is associated with molecular or pathological features of colorectal carcinoma tissues. As a result, SEMS placement was significantly associated with venous invasion ($P < 0.01$), but not with the other features examined, including tumor size, disease stage, mutation status, and lymphatic invasion. In both the univariable and multivariable models with adjustment for potential factors including tumor location, histological type, and American Joint Committee on Cancer-pT stage, SEMS placement was significantly associated with severe venous invasion ($P < 0.01$). For the outcome category of severe venous invasion, the multivariable odds ratio for SEMS placement relative to transanal tube placement was 19.4 (95% confidence interval: 5.24–96.2).

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INTRODUCTION

Colorectal cancer is the third most common cancer in both men and women worldwide[1]. Despite remarkable advances in conventional multidisciplinary therapies for colorectal cancer, including surgery[2], radiotherapy, chemotherapy, and immunotherapy, improvements in clinical outcomes have been limited. Further developments of innovative treatment strategies are aggressively being sought, especially for colorectal cancer with complications, such as obstruction, perforation, and hemorrhage [3]. A considerable number of colorectal cancer patients present with a colonic obstruction, and the incidence is reported as high as 30%[4]. As colonic obstruction might endanger the life of patients, emergent decompression is urgently required. Emergency surgery might be associated with increased morbidity, mortality, stoma rate, and oncological suboptimal resection[4-6]. Therefore, a bridge to surgery approach could be a reasonable treatment strategy to allow for one-stage, or elective resection for obstructive colorectal cancer patients[7].

Self-expanding metal stents (SEMSs) have been used worldwide to rescue intestinal obstruction caused by colorectal cancer as well as benign diseases. Accumulating evidence suggests that SEMS placement results in marked advantages in short-term outcomes including the primary anastomosis rate, postoperative complications, and hospital stay after elective surgery because of patients' good general condition and adequate bowel preparation before surgery[8-11]. SEMSs might have a critical role of serving as a bridge to surgery for resectable colorectal carcinomas. Despite the efficacy and feasibility of SEMS placement in patients with obstructive colorectal cancer, there are several clinical concerns regarding SEMS placement. One of the major concerns is the risk of worse molecular or pathological malignancy by mechanical damage and pressure to the primary tumor by SEMS placement. In an *in vivo* experiment, peritoneal carcinomatosis and liver metastasis were more frequently observed in the stent group[12]. Additionally, human studies have indicated increased numbers of circulating tumor cells after SEMS placement but not after transanal decompression tube placement[13-15]. Based this evidence, we hypothesized that SEMS placement is associated with molecular or pathological malignancy in colorectal carcinoma tissues.

To test this hypothesis, we used a nonbiased molecular pathological epidemiology database of patients with obstructive colorectal cancer, and examined the molecular and pathological features of tumor tissue according to the decompression methods. Unlike previous studies[16,17], we first diagnosed lymphatic invasion (absent, minimal, moderate, or severe) and venous invasion (absent, minimal, moderate, or severe) in detail based on the Japanese Classification of Colorectal Carcinoma [18], and investigated the association between SEMS placement and molecular or pathological malignancy. We argue that the use of transdisciplinary integrated analyses to obtain a better understanding of the interaction between the decompression technique and tumor tissue characteristics will significantly help in the development of new treatment strategies for obstructive colorectal cancer.

MATERIALS AND METHODS

Study population

This study included 102 consecutive patients with obstructive colorectal cancer who underwent emergent colonic decompression at the National Hospital Organization Kumamoto Medical Center from July 2012 to December 2020. The main inclusion criteria were an age of > 18 years, histological confirmation of colorectal adenocarcinoma before or after the operation, no other active malignancy, and performance of emergent colonic decompression followed by surgery. The exclusion criteria were neoadjuvant chemotherapy and/or radiotherapy, perforation, peritonitis. The decompression method for each case was determined by tumor board. SEMS or transanal decompression tube placement was performed under both endoscopic and fluoroscopic guidance for obstructive colorectal cancer (CROSS scale 0, 1, or 2)[19]. Patients underwent cleansing enema for bowel preparation and received analgesia and sedation. The stent size and length were chosen according to the measured length of the obstruction. Tumor staging was performed according to the American Joint Committee on Cancer (AJCC) TNM classification (7th edition)[20]. Two institutional pathologists diagnosed histopathological differentiation (well, moderate, or others), lymphatic invasion (absent, minimal, moderate, or severe), and venous invasion (absent, minimal, moderate, or severe) based on the Japanese Classification of Colorectal Carcinoma[18]. Postoperative complications were recorded and graded as defined by the Clavien–Dindo classification system[21]. The term "prognostic marker" is used throughout this article according to the REMARK Guidelines[22].

This study was approved by the Human Ethics Review Committee of the National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan (institutional ethics committee number: 1061). The requirement for written informed consent was waived in view of the retrospective nature of the study.

Statistical analysis

All statistical analyses were conducted using the JMP program (version 10, SAS Institute, Cary, NC, United States). All *P* values were two-sided, and the two-sided α level of 0.05 was used for all testing.

Our primary analysis (hypothesis testing) involved examination of the associations of the decompression method used (SEMS *vs* transanal tube; as a predictor variable) with lymphatic invasion and venous invasion. All other analyses, including assessments of odds ratios (ORs), represented secondary analyses. We performed multivariable logistic regression analyses to control for potential confounders. The multivariable logistic regression model included variables showing a univariable association ($P < 0.05$) with lymphatic invasion or venous invasion from the decompression method (transanal tube *vs* SEMS), age (continuous), sex (female *vs* male), tumor location (cecum to transverse colon *vs* descending to sigmoid colon *vs* rectum), waiting period (continuous), tumor size (continuous), histological type (well differentiated *vs* moderately differentiated *vs* others), AJCC-pT (T2/T3 *vs* T4), and mutation (absent *vs* present).

To compare characteristics across strata of decompression methods, we used the chi-square test for categorical variables, and an analysis of variance, assuming equal variances for continuous variables. Each of the cross-sectional analyses was secondary.

Overall survival was defined as the time between the operation date and the date of death. Disease-free survival was defined as the time between the operation date and the date of recurrence. The survival time distributions were determined by the Kaplan–Meier method using a log-rank test.

RESULTS

Decompression methods and clinical, pathological, and molecular characteristics

Among the 102 patients with obstructive colorectal cancer in the nonbiased independent database, 53% were women and the median age was 72.6 years. The most frequent tumor location was descending to sigmoid colon (65 patients, 64%), followed by the rectum (21 patients, 21%) and cecum to transverse colon (16 patients, 16%). Table 1 summarizes the clinical, pathological, and molecular features of the

Table 1 Clinical and pathological features of patients with colorectal cancer according to decompression methods

Characteristic[1]	All cases (*n* = 102)	Decompression methods		*P* value[2]
		Transanal tube (*n* = 76)	SEMS (*n* = 26)	
Sex, *n* (%)				0.91
Female	54 (53)	40 (53)	14 (54)	
Male	48 (47)	36 (47)	12 (46)	
Age, mean ± SD (years)	72.6 ± 12.5	71.7 ± 12.9	75.1 ± 11.1	0.24
Tumor location, *n* (%)				0.24
Cecum to transverse colon	16 (16)	13 (17)	3 (12)	
Descending to sigmoid colon	65 (64)	45 (59)	20 (77)	
Rectum	21 (21)	18 (24)	3 (12)	
Tumor size, mean ± SD (mm)	40.7 ± 16.2	39.0 ± 14.9	45.4 ± 19.3	0.086
Time from decompression to operation, mean ± SD (days)	13.6 ± 12.9	12.0 ± 7.6	18.2 ± 21.7	0.035
Histological type, *n* (%)				0.35
Well	29 (28)	19 (25)	10 (38)	
Moderate	67 (66)	53 (70)	14 (54)	
Mucinous, poor, or signet-ring cell	6 (5.9)	4 (5.3)	2 (7.7)	
T stage (depth of tumor invasion), *n* (%)				0.57
T1 (submucosa)	-	-	-	
T2 (muscularis propria)	1 (1.0)	-	1 (3.9)	
T3 (subserosa)	67 (66)	54 (71)	13 (50)	
T4 (serosa or other organs)	34 (33)	22 (29)	12 (46)	
N stage (number of positive lymph nodes), *n* (%)				0.54
N0 (0)	49 (48)	36 (47)	13 (50)	
N1 (1-3)	39 (38)	28 (37)	11 (42)	
N2 (4-)	14 (14)	12 (16)	2 (7.7)	
AJCC disease stage, *n* (%)				0.40
I	1 (1.0)	-	1 (3.9)	
II	42 (41)	31 (41)	11 (42)	
III	36 (35)	27 (36)	9 (35)	
IV	23 (23)	18 (24)	5 (19)	
Mutation status, *n* (%)				0.51
KRAS mutated	34 (43)	26 (47)	8 (33)	
NRAS mutated	3 (3.8)	2 (3.6)	1 (4.2)	
BRAF mutated	0 (0)	0 (0)	0 (0)	
Absent	42 (53)	27 (49)	15 (63)	

[1]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of decompression methods.
[2]We used the chi-square test to compare categorical variables and analysis of variance to compare continuous variables. We adjusted the two-sided α level to 0.05.
AJCC: American Joint Committee on Cancer; SEMS: Self-expanding metal stent.

patients stratified according to decompression methods. Seventy-six (75%) patients underwent transanal tube placement, and 26 (25%) patients underwent SEMS placement. SEMS placement was significantly associated with a longer time between decompression and surgery (P = 0.035), but not with the other features examined, including tumor size, disease stage, and mutation status (all P > 0.08).

Table 2 summarizes the perioperative features of the patients stratified according to decompression methods. SEMS placement was significantly associated with a higher chance of reconstruction (P = 0.011), but not with the other features examined, including operation method, procedure, lymph node dissection, and short-term outcomes (all P > 0.07).

Decompression methods and lymphatic or venous invasion

Table 3 shows the distribution of patients according to the decompression methods and lymphatic invasion or venous invasion. SEMS placement was significantly associated with severe venous invasion (P < 0.0001). Table 4 shows the distribution of colorectal cancer cases according to decompression methods (transanal tube *vs* SEMS) and lymphatic or venous invasion in strata of AJCC-pT stage or tumor location. A similar association of SEMS placement with severe venous invasion was observed (P < 0.11).

Logistic regression analyses between decompression methods and venous invasion

To test our primary hypothesis, we used a logistic regression analysis to assess the association of the decompression method (SEMS *vs* transanal tube) with the degree of venous invasion (Table 5). In both the univariable and multivariable models, SEMS placement was significantly associated with severe venous invasion (P < 0.0001). For the outcome category of venous invasion, the univariable OR was 20.9 [95% confidence interval (CI): 5.78–101] for SEMS placement relative to transanal tube placement, and the multivariable OR was 19.4 (95%CI: 5.24–96.2). Similar findings were observed in the sensitivity analyses, in which we performed a multivariable analysis with adjustment for potential factors including tumor location, histological type, and AJCC-pT stage (multivariable OR: 36.7; 95%CI: 7.89–259; P < 0.0001). AJCC-pT was significantly associated with severe venous invasion in only the univariable model (P = 0.021), and the univariable OR was 3.72 (95%CI: 1.22–12.2) for AJCC-pT4 relative to AJCC-pT2/T3.

Among SEMS group, the waiting period for surgery did not have any association with venous invasion. For the outcome category of venous invasion, the univariable OR was 0.86 (95%CI: 0.46–1.14; P = 0.32) for waiting period (for 1-wk increment).

Exploratory analyses for the influence of stent diameter on lymphatic and venous invasion

As an exploratory analysis, we determined the influence of stent diameter on lymphatic and venous invasion (Table 6). A larger stent was significantly associated with venous invasion (P < 0.0001), and was possibly associated with lymphatic invasion (P = 0.055).

Decompression methods and long-term survival

As exploratory analyses, a Kaplan-Meier analysis was conducted to assess the influence of SEMS placement on long-term survival. No significant differences of disease-free survival and overall survival were observed (P = 0.56 for disease-free survival, P = 0.60 for overall survival).

DISCUSSION

Evidence indicates marked advantages in short-term outcomes by SEMS placement in patients with obstructive colorectal cancer because of these patients' good general condition and adequate bowel preparation before surgery[8,9]. Notably, other emerging evidence points to a link between SEMS placement and an increase in the number of circulating tumor cells by mechanical damage and pressure to the primary tumor[12-15]. However, the associations of SEMS placement with the molecular and pathological features of colorectal carcinoma tissues remain to be elucidated. The present study was performed to test the hypothesis that SEMS placement is associated with molecular or pathological malignancy in colorectal carcinoma tissues. We used a nonbiased molecular pathological epidemiology database of patients with obstructive colorectal cancer, and showed for the first time that SEMS placement is independently associated with severe venous invasion in colorectal cancer tissue. Although no significant differences of prognoses were observed, our findings suggest a possible influence of SEMS placement on pathological findings.

A growing body of evidence highlights associations between SEMS placement and short-term clinical outcomes among patients with obstructive colorectal cancer. A systematic review of randomized controlled trials showed that 81% of SEMS placements were technically successful, with 76% of patients achieving restoration of gastrointestinal function[23]. Additionally, a meta-analysis showed that SEMS placement helped to maintain quality of life by allowing food intake and temporal discharge, promoted laparoscopic one-stage surgery without stoma creation, and had morbidity and mortality rates equivalent to those of transanal decompression tube placement[9]. SEMS placement might decrease the rate of permanent stomas, especially in elderly patients[8]. Emerging evidence indicates the safety and feasibility of minimally invasive surgery combined with stent insertion for malignant colonic obstruction[24]. Collectively, colonic stenting followed by laparoscopy is safe and effective with high success rates and low complication rates. However, several points remain to be investigated, such as

Table 2 Perioperative features of patients with colorectal cancer according to decompression methods

Characteristic[1]	All cases (*n* = 102)	Decompression methods		*P* value[2]
		Transanal tube (*n* = 76)	SEMS (*n* = 26)	
Operation method, *n* (%)				0.31
Open	54 (53)	38 (50)	16 (62)	
Laparoscopy	48 (47)	38 (50)	10 (38)	
Conversion to laparotomy, *n* (%)				0.072
Absent	47 (98)	38 (100)	9 (90)	
Present	1 (2.1)	-	1 (10)	
Procedure, *n* (%)				0.17
Colectomy	58 (57)	44 (58)	14 (54)	
Anterior resection	37 (36)	25 (33)	12 (46)	
Hartmann procedure	5 (4.9)	5 (6.6)	-	
Abdominoperineal resection (Miles' operation)	2 (2.0)	2 (2.6)	-	
Lymph node dissection, *n* (%)				0.35
D1	3 (2.9)	3 (4.0)	-	
D2	10 (9.8)	8 (11)	2 (7.7)	
D3	89 (87)	65 (86)	24 (92)	
Reconstruction (except 2 abdominoperineal resection cases), *n* (%)				0.011
Absent	10 (10)	10 (14)	-	
Present	90 (90)	64 (86)	26 (100)	
Number of harvested lymph nodes, mean ± SD	21.6 ± 12.0	21.5 ± 11.8	21.7 ± 12.6	0.97
Operation time, mean ± SD (min)	241 ± 80	234 ± 79	263 ± 79	0.12
Blood loss, mean ± SD (g)	224 ± 364	229 ± 375	212 ± 336	0.84
Clavien-Dindo classification, *n* (%)				0.22
0	78 (76)	58 (76)	20 (77)	
1	5 (4.9)	5 (6.6)	-	
2	11 (11)	8 (11)	3 (12)	
3	7 (7.7)	5 (6.6)	2 (7.7)	
4	-	-	-	
5	1 (1.0)	-	1 (3.9)	
Postoperative hospitalization, mean ± SD (days)	18.8 ± 15.1	19.3 ± 17.0	17.2 ± 6.7	0.53
Postoperative chemotherapy, *n* (%)				0.36
Absent	51 (50)	36 (47)	15 (58)	
Present	51 (50)	40 (53)	11 (42)	

[1]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of decompression methods.
[2]We used the chi-square test to compare categorical variables and analysis of variance to compare continuous variables. We adjusted the two-sided α level to 0.05.
SEMS: Self-expanding metal stent.

postoperative chemotherapy[25], the SEMS-related perforation rate (5.0%–8.9%)[8,23,26], perforation-related recurrence[26], the SEMS diameter[27], and the optimal timing from stent placement to surgery [28,29].

Long-term survival of patients with complicated colorectal cancer remains poor despite advances in surgical techniques. Additionally, how SEMS placement impacts long-term survival compared with

Table 3 Pathological features of patients with colorectal cancer according to decompression methods

Characteristic[1]	All cases (*n* = 102)	Decompression methods		*P* value[2,3]
		Transanal tube (*n* = 76)	SEMS (*n* = 26)	
Lymphatic invasion, *n* (%)				0.12 (0.020)
Absent	11 (11)	10 (13)	1 (3.9)	
Minimal	41 (40)	33 (43)	8 (31)	
Moderate	32 (31)	23 (30)	9 (35)	
Severe	18 (18)	10 (13)	8 (31)	
Venous invasion, *n* (%)				< 0.0001 (0.0002)
Absent	19 (19)	17 (22)	2 (7.7)	
Minimal	45 (44)	37 (49)	8 (31)	
Moderate	23 (23)	19 (25)	4 (15)	
Severe	15 (15)	3 (4.0)	12 (46)	

[1]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of decompression methods.
[2]We used the chi-square test to compare as categorical variables. We adjusted the two-sided α level to 0.05.
[3]We used the Mann-Whitney U test to compare as nonparametric continuous variables. We adjusted the two-sided α level to 0.05.
SEMS: Self-expanding metal stent.

other procedures, including diverting stomas, transanal tubes, and emergency surgery, remains controversial. A retrospective single- or multicenter observational study and two meta-analyses showed no significant difference in long-term survival between the SEMS group and emergency surgery group among patients with obstructive left-sided colorectal cancer[30-33]. Additionally, one randomized controlled trial showed no prognostic difference between the two groups[34]. One retrospective observational study revealed no significant differences in long-term outcomes between patients with obstructive colorectal cancer who underwent SEMS placement and transanal decompression tube placement as a bridge to surgery[35]. In the current study, no significant differences of disease-free survival and overall survival were observed between SEMS and transanal tube groups. A national, population-based cohort study using propensity score matching suggested that SEMS placement has intermediate-term oncologic outcomes similar to those of a decompressing stoma as a bridge to resection of left-sided obstructive colon cancer[36]. While, a French surgical association multicenter cohort study utilizing a propensity score analysis suggested that SEMS placement might be associated with a worse prognosis than a diverting stoma or immediate surgery for obstructive left-sided colorectal cancer[37,38]. The CODOMO study showed that transanal decompression tube placement might be associated with a worse prognosis than surgery for obstructive left-sided colorectal cancer[30]. For obstructive right-sided colorectal cancer, another population-based observational study demonstrated that the prognosis was significantly better in the decompression tube group than in the SEMS group [39]. SEMS-related perforation or an increased bridging interval to surgery might be a significant risk factor for systemic recurrence[26,29]. With respect to operation methods, laparoscopic surgery after stent placement for obstructive colon cancer might be performed safely with long-term outcomes comparable with those of open surgery[40]. The diameter of the colonic stent might not impact long-term survival[27]. Further research is warranted to investigate the prognostic role of SEMS placement in obstructive colorectal cancer compared with other procedures.

Dissemination of tumor cells has been a major concern in patients who undergo SEMS placement for obstructive colorectal cancer, and several experimental studies have focused on circulating tumor cells in the bloodstream. In 2007, an increase in the level of CK20 mRNA in the peripheral circulation was confirmed after endoscopic colonic stent insertion in patients with colorectal cancer[41]. In an *in vivo* study using a mouse model, peritoneal carcinomatosis and liver metastasis were more frequently observed in the stent group[12]. Moreover, in patients with obstructive colorectal cancer, the plasma levels of cell-free DNA and circulating tumor DNA increased after SEMS placement but not after transanal decompression tube placement; this suggests an oncological risk of SEMS placement in terms of molecular analysis[13-15]. The no-touch isolation technique, which was first proposed in 1952[42], gives first priority to central vascular ligation followed by mobilization of the tumor-bearing segment of the colon. This technique might reduce the spread of circulating tumor cells from the primary tumor site to other organs by ligation of blood vessels first. One retrospective study showed prognostic improvement by the no-touch isolation technique[43], but a large-scale randomized controlled trial failed to confirm the superiority of the no-touch isolation technique in patients with colorectal cancer [44]. In the current study, we found an association of SEMS placement with high severe invasion, but we

Table 4 Pathological features of patients with colorectal cancer according to decompression methods in strata of American Joint Committee on Cancer-pT stage or tumor location

Characteristic[1]	All cases (*n* = 102)	Decompression methods		*P* value[2,3]
		Transanal tube (*n* = 76)	SEMS (*n* = 26)	
Lymphatic invasion				
AJCC-pT2/T3 cases, *n* (%)				0.024 (0.036)
Absent	8 (12)	8 (15)	-	
Minimal	31 (46)	25 (46)	6 (43)	
Moderate	20 (29)	17 (31)	3 (21)	
Severe	9 (13)	4 (7.4)	5 (36)	
AJCC-pT4 cases, *n* (%)				0.53 (0.56)
Absent	3 (8.8)	2 (9.1)	1 (8.3)	
Minimal	10 (29)	8 (36)	2 (17)	
Moderate	12 (35)	6 (27)	6 (50)	
Severe	9 (26)	6 (27)	3 (25)	
Venous invasion				
AJCC-pT2/T3 cases, *n* (%)				0.0031 (0.0025)
Absent	13 (19)	12 (22)	1 (7.1)	
Minimal	37 (54)	32 (59)	5 (36)	
Moderate	12 (18)	9 (17)	3 (21)	
Severe	6 (8.8)	1 (1.9)	5 (36)	
AJCC-pT4 cases, *n* (%)				0.0077 (0.042)
Absent	6 (18)	5 (23)	1 (8.3)	
Minimal	8 (24)	5 (23)	3 (25)	
Moderate	11 (32)	10 (45)	1 (8.3)	
Severe	9 (26)	2 (9.1)	7 (58)	
Lymphatic invasion				
Cecum to transverse colon cases, *n* (%)				0.21 (0.088)
Absent	3 (19)	3 (23)	-	
Minimal	7 (44)	6 (46)	1 (33)	
Moderate	4 (25)	4 (31)	-	
Severe	2 (13)	-	2 (67)	
Descending to rectum, *n* (%)				0.40 (0.096)
Absent	8 (9.3)	7 (11)	1 (4.4)	
Minimal	34 (40)	27 (43)	7 (30)	
Moderate	28 (33)	19 (30)	9 (39)	
Severe	16 (19)	10 (16)	6 (26)	
Venous invasion				
Cecum to transverse colon cases, *n* (%)				0.10 (0.078)
Absent	5 (31)	5 (38)	-	
Minimal	6 (38)	5 (38)	1 (33)	
Moderate	2 (13)	2 (15)	-	
Severe	3 (19)	1 (7.7)	2 (67)	

Descending to rectum, *n* (%)				0.0001 (0.0012)
Absent	14 (16)	12 (19)	2 (8.7)	
Minimal	39 (45)	32 (51)	7 (30)	
Moderate	21 (24)	17 (27)	4 (17)	
Severe	12 (14)	2 (3.2)	10 (43)	

[1]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of decompression methods.
[2]We used the chi-square test to compare as categorical variables. We adjusted the two-sided α level to 0.05.
[3]We used the Mann-Whitney U test to compare as nonparametric continuous variables. We adjusted the two-sided α level to 0.05.
AJCC: American Joint Committee on Cancer; SEMS: Self-expanding metal stent.

Table 5 Logistic regression analyses to assess the association of decompression method (predictor) with severe venous invasion (outcome)

Model for severe venous invasion (*n* = 102, as a binary outcome variable)	Univariable		Multivariable[1]		Multivariable[2]	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Decompression methods						
Transanal tube	1 (reference)	< 0.0001	1 (reference)	< 0.0001	1 (reference)	< 0.0001
SEMS	20.9 (5.78-101)		19.4 (5.24-96.2)		36.7 (7.89-259)	
Age (for 10-yr increment)	1.29 (0.82-2.20)	0.28				
Sex						
Female	1 (reference)	0.60				
Male	1.34 (0.44-4.14)					
Tumor location						
Cecum to transverse colon	1 (reference)	0.27			1 (reference)	0.27
Descending to sigmoid colon	0.88 (0.23-4.31)				0.38 (0.05-2.60)	
Rectum	0.22 (0.01-1.90)				0.11 (0.003-1.58)	
Waiting period (for 1-wk increment)	0.91 (0.47-1.22)	0.64				
Tumor size (for 10-mm increment)	1.10 (0.78-1.49)	0.55				
Histological type						
Well	1 (reference)	0.21			1 (reference)	0.065
Moderate	2.65 (0.65-17.9)				7.27 (1.27-64.5)	
Mucinous, poor, or signet-ring cell	6.75 (0.66-72.0)				10.7 (0.48-342)	
AJCC-pT						
T2/T3	1 (reference)	0.021	1 (reference)	0.084	1 (reference)	0.082
T4	3.72 (1.22-12.2)		3.17 (0.86-12.6)		3.76 (0.85-19.4)	
Mutation						
Absent	1 (reference)	0.81				
Present (*KRAS*, *NRAS*)	1.16 (0.33-4.07)					

[1]The multivariable logistic regression model included the decompression method (transanal tube *vs* SEMS), and AJCC-pT (T2/T3 *vs* T4).
[2]The multivariable logistic regression model included the decompression method (transanal tube *vs* SEMS), tumor location (cecum to transverse colon *vs* descending to sigmoid colon *vs* rectum), histological type (well-differentiated vs. moderately differentiated *vs* others), and AJCC-pT (T2/T3 *vs* T4).
AJCC: American Joint Committee on Cancer; CI: Confidence interval; OR: Odds ratio; SEMS: Self-expanding metal stent.

observed no significant differences of long-term survivals between two groups. Our findings need to be confirmed in future multicenter studies with a larger cohort.

Table 6 Pathological features of patients with colorectal cancer according to decompression methods (transanal tube *vs* 18-mm stent *vs* 22-mm stent)

Characteristic[1]	All cases (*n* = 102)	Decompression methods			*P* value[2,3]
		Transanal tube (*n* = 76)	18 mm stent (*n* = 11)	22 mm stent (*n* = 15)	
Lymphatic invasion, *n* (%)					0.055 (0.0060)
Absent	11 (11)	10 (13)	1 (9.1)	-	
Minimal	41 (40)	33 (43)	5 (45)	3 (20)	
Moderate	32 (31)	23 (30)	4 (36)	5 (33)	
Severe	18 (18)	10 (13)	1 (9.1)	7 (47)	
Venous invasion, *n* (%)					< 0.0001 (0.0006)
Absent	19 (19)	17 (22)	2 (18)	-	
Minimal	45 (44)	37 (49)	3 (27)	5 (33)	
Moderate	23 (23)	19 (25)	1 (9.1)	3 (20)	
Severe	15 (15)	3(4.0)	5 (45)	7 (47)	

[1]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of decompression methods.
[2]We used the chi-square test to compare as categorical variables. We adjusted the two-sided α level to 0.05.
[3]We used the Mann-Whitney U test to compare as nonparametric continuous variables. We adjusted the two-sided α level to 0.05.

We acknowledge several limitations in our study. First, the sample size was small, and this was a retrospective observational study at a single center. However, our findings are quite significant despite of small sample size. Because the optimal treatment strategy for obstructive colorectal cancer has not been established, our findings should be verified with a larger cohort in a multi-institutional study. Second, the current study was cross-sectional in nature, and the exact mechanisms that underlie the relationship between SEMS placement and severe venous invasion remain uncertain. Our hypothesis was based on several lines of experimental and population-based evidence indicating that mechanical damage and pressure to the primary tumor by SEMS placement increase venous invasion. Comparison of the pathological features between before and after SEMS placement is quite challenging, and the current study which considered the tumor stage and molecular and pathological features must be valuable. Third, we did not investigate the relationship between venous invasion and circulating tumor cells in the bloodstream. Fourth, the pathological findings including the degree of venous invasion were diagnosed based on the Japanese Classification of Colorectal Carcinoma by two pathologists[18], but the diagnosis is assessed by subjective methods. That is another limitation. Future studies are needed to confirm our findings and examine the association of SEMS placement with molecular and pathological features and long-term survival of patients with obstructive colorectal cancer.

A major strength of our study is that it used a molecular pathological epidemiology[45,46] database of patients with colorectal cancer, forming an independent cohort. This database integrates epidemiologic data, clinicopathologic features, and tumor molecular features including the *KRAS*, *BRAF*, or *NRAS* mutation status in colorectal cancer tissue. Our multidisciplinary integrated study based on this human-population colorectal cancer database enabled us to rigorously investigate the association of SEMS placement with the molecular and pathological features of colorectal cancer tissues; we utilized multivariable logistic regression models after controlling for multiple potential confounders such as disease stage, tumor location, and tumor molecular features.

CONCLUSION

In conclusion, we have herein shown that SEMS placement might be associated with severe venous invasion in colorectal cancer tissue, providing an impetus for further investigation of the potential interactive roles of SEMS placement and pathological alterations in colorectal cancer tissues. Validation of our findings may provide insights for further investigations on strategies for obstructive colorectal cancer.

ARTICLE HIGHLIGHTS

Research background

Experimental studies suggest that self-expanding metal stents (SEMSs) enhance the aggressive behavior of obstructive colorectal cancer.

Research motivation

The influence of SEMS placement on pathological alterations remains to be elucidated.

Research objectives

This study aimed to determine whether SEMS placement is associated with molecular or pathological features of colorectal carcinoma tissues.

Research methods

Using a nonbiased molecular pathological epidemiology database of patients with obstructive colorectal cancers, we examined the association of SEMS placement with molecular or pathological feature.

Research results

SEMS placement was significantly associated with venous invasion ($P < 0.01$), but not with the other features examined, including tumor size, disease stage, mutation status, and lymphatic invasion. In both the univariable and mult-ivariable models with adjustment for potential factors including tumor location, histological type, and American Joint Committee on Cancer-pT stage, SEMS placement was significantly associated with severe venous invasion ($P < 0.01$).

Research conclusions

SEMS placement might be associated with severe venous invasion in colorectal cancer tissue.

Research perspectives

Future studies are needed to confirm our findings and examine the association of SEMS placement with pathological features and long-term survival of patients with obstructive colorectal cancer.

FOOTNOTES

Author contributions: Kosumi K, Mima K, Miyanari N and Baba H participated in study conception and design; All authors participated in data acquisition; Kosumi K and Mima K performed the statistical analyses and analyzed the data; Miyanari N and Baba H supervised the work; Kosumi K, Mima K, Miyamoto Y, Miyanari N and Baba H were the major contributors to manuscript preparation; All authors contributed to the manuscript, critically revised it, and approved the final version.

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META-ANALYSIS

Antibiotic prophylaxis to prevent complications in endoscopic retrograde cholangiopancreatography: A systematic review and meta-analysis of randomized controlled trials

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Abstract

BACKGROUND

The prophylactic use of antibiotics in endoscopic retrograde cholangiopancreatography (ERCP) is still controversial.

AIM

To assess whether antibiotic prophylaxis reduces the rates of complications in patients undergoing elective ERCP.

METHODS

This systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. A comprehensive search of multiple electronic databases was performed. Only randomized controlled trials were included. The outcomes analyzed included bacteremia, cholangitis, sepsis, pancreatitis, and mortality. The risk of bias was assessed by the Cochrane revised Risk-of-Bias tool for randomized controlled trials. The quality of evidence was assessed by the Grading of Recommendation Assessment, Development, and Evaluation. Meta-analysis was performed using the Review Manager 5.4 software.

RESULTS

Ten randomized controlled trials with a total of 1757 patients that compared the use of antibiotic and non-antibiotic prophylaxis in patients undergoing elective ERCP were included. There was no significant difference between groups regarding incidence of cholangitis after ERCP [risk difference (RD) = -0.02, 95% confidence interval (CI): -0.05, 0.02, P = 0.32], cholangitis in patients with suspected biliary obstruction (RD = 0.02, 95%CI: -0.08 to 0.13, P = 0.66), cholangitis on intravenous antibiotic prophylaxis (RD = -0.02, 95%CI: -0.05 to 0.01, P = 0.25), septicemia (RD = -0.02, 95%CI: -0.06 to 0.01, P = 0.25), pancreatitis (RD = -0.02, 95%CI: -0.06 to 0.01, P = 0.19), and all-cause mortality (RD = 0.00, 95%CI: -0.01 to 0.01, P = 0.71]. However, the antibiotic prophylaxis group presented a 7% risk reduction in the incidence of bacteremia (RD= -0.07, 95%CI: -0.14 to -0.01, P = 0.03).

CONCLUSION

The prophylactic use of antibiotics in patients undergoing elective ERCP reduces the risk of bacteremia but does not appear to have an impact on the rates of cholangitis, septicemia, pancreatitis, and mortality.

Key Words: Endoscopy; Antibiotics; Endoscopic retrograde cholangiopancreatography; Cholangitis; Infection

Core Tip: There is controversy about antibiotic prophylaxis in patients undergoing elective endoscopic retrograde cholangiopancreatography. This is a systematic review and meta-analysis based on randomized controlled trials that analyzed whether the use of antibiotic prophylaxis is beneficial in preventing complications after this procedure. Outcomes evaluated include the rate of cholangitis, bacteremia, sepsis, pancreatitis, and mortality. Based on this meta-analysis, antibiotic prophylaxis reduces the risk of bacteremia but does not impact the rate of cholangitis, septicemia, pancreatitis, and mortality.

Citation: Merchan MFS, de Moura DTH, de Oliveira GHP, Proença IM, do Monte Junior ES, Ide E, Moll C, Sánchez-Luna SA, Bernardo WM, de Moura EGH. Antibiotic prophylaxis to prevent complications in endoscopic retrograde cholangiopancreatography: A systematic review and meta-analysis of randomized controlled trials. *World J Gastrointest Endosc* 2022; 14(11): 718-730
URL: https://www.wjgnet.com/1948-5190/full/v14/i11/718.htm
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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most technically challenging procedures in digestive endoscopy, associated with high rates of adverse events (AEs), reported in up to 18.9% of cases[1-3]. The most common adverse events include bacteremia, cholangitis, and pancreatitis occurring in about 6.5% to 18.0%[4], 3.0%[5,6], and 5.5%[7] respectively.

Prophylactic antibiotics are used with the intent to prevent complications of ERCP. Their use is controversial and is currently being recommended in patients with incomplete biliary drainage, such as hilar tumors and primary sclerosing cholangitis[8] due to the potential risk of septic complications from the manipulation of obstructed bile ducts that could serve as a source of bacterial colonization, thus increasing the risk of bacteremia[4] and cholangitis.

The European Society for Gastrointestinal Endoscopy[9] and the American Society for Gastrointestinal Endoscopy[10] guidelines do not recommend routine antibiotics prophylaxis before elective ERCP in low-risk groups. Both guidelines recommend antibiotic prophylaxis in specific situations such as liver transplant[11], severe neutropenia, the impossibility of complete biliary drainage, use of cholangioscopy[12], and in patients with primary sclerosing cholangitis[13].

Although both guidelines regarding antibiotic prophylaxis for ERCP do not recommend its routine use, the data to support this recommendation is not robust. Therefore, we performed a systematic review and meta-analysis to evaluate whether the use of antibiotic prophylaxis has an impact on the rate of complications related to elective ERCP.

MATERIALS AND METHODS

Protocol and registration

The study protocol was registered in the International Prospective Register of Systematic Reviews under the file number CRD42022289127 and was approved by the Ethics Committee of Hospital das Clínicas, Faculty of Medicine at The University of São Paulo. This systematic review and meta-analysis were performed in conformity with the recommendations from the Cochrane Handbook of Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines[14].

Information source and literature search

Individualized searches of multiple electronic databases (MEDLINE, Embase, Cochrane, LILACS, clincaltrials.gov, and gray literature) were performed based upon a standardized protocol from their inception through February 2022. The search included the following Medical Subject Headings: "(Endoscopy OR Endoscopic) AND (Anti-Bacterial Agents OR Antibacterial Agents OR Antibacterial Agent OR Antibiotics OR Antibiotic) AND [prophylaxis OR preventive OR (prevention and control)]." A further literature search was conducted with the Reference Citation Analysis engine, an artificial intelligence technology-based open multidisciplinary citation analysis database (https://www.referencecitationanalysis.com). Following a search within the Reference Citation Analysis database no further studies were identified that fit our inclusion criteria.

Study selection

Two researchers independently conducted the eligibility screening. From the initial search results, duplicate articles were excluded, and the titles and abstracts of all potentially relevant studies were screened for eligibility. Any disagreements were settled by consensus or by consulting a third reviewer.

Only randomized controlled trials (RCTs) comparing antibiotic prophylaxis *vs* no use of prophylactic antibiotics in patients undergoing elective ERCP regardless of publication date or language were considered.

Patients with cholangitis or other types of active infection, history of antibiotic allergy, and immunosuppressed were excluded.

Data extraction and definitions

Items included in data extraction were first author, year of publication, study design, and outcomes of interest such as cholangitis, bacteremia, septicemia, pancreatitis, and mortality. We defined cholangitis as the presence of fever (> 38.5 °C), abdominal pain, leukocytosis, and elevated C-reactive protein. Blood cultures and bile samples were taken to evaluate for bacteremia. Bacteremia was defined as a positive culture with no evidence of systemic inflammatory response. Blood culture samples were taken before and after the ERCP procedure and in the presence of fever. In one of the studies a blood culture was obtained only if the patients presented signs of cholangitis. Septicemia was defined as a positive blood culture with systemic inflammatory response (fever, hypotension, tachycardia, leukocytosis > 10 g/dL, leukopenia < 3 g/L, and chills). The diagnosis of pancreatitis was based on clinical findings, increased serum amylase or lipase three-fold or more over the normal upper range. Antibiotic prophylaxis is defined as administering antibiotics to patients who underwent invasive procedures without evidence of infection at the time of the procedure. The goal of such prophylaxis was to reduce the risk of infection.

Risk of bias and quality of evidence

We assessed the risk of bias using the Cochrane Risk of Bias tool version 2[14].

The quality of evidence was assessed utilizing the objective criteria from Grading Recommendations Assessment, Development, and Evaluation for each of the prespecified results and outcomes using the GRADEpro-Guideline Development Tool software (McMaster University, 2015; Evidence Prime, Inc., Ontario, Canada)[15].

Statistical analysis

Continuous variables were analyzed using mean difference and standard deviation with a 95% confidence interval. For categorical variables, the risk difference (RD) was used, with a 95% confidence interval. The RD and mean difference were considered statistically significant at a value of $P \leq 0.05$. If a study provided medians and interquartiles or ranges, they were attributed to means, and standard deviation was estimated as described by the McGrath *et al*[16] method.

The inconsistency index was evaluated using the Higgins I^2 method[17], in which the presence of heterogeneity can be observed. The random effect was used for all analyses. The meta-analysis was performed using the RevMan software (Review Manager Software version 5.4-Cochrane Collaboration Copyright© 2020).

RESULTS

Study selection

The initial search strategy identified 5594 articles. Through the evaluation by title and abstract, 2999 articles were excluded, yielding 165 studies. Of these, 10 RCTs, including 1757 patients (843 in the control group and 914 in the intervention group) met the eligibility criteria and were included in this systematic review and meta-analysis (Figure 1). The characteristics and results of the included studies are summarized in Table 1.

Risk of bias and quality of evidence

All 10 studies[18-27] were RCTs. Three studies presented a low risk bias[19,20,22]. Three studies presented a moderate risk of bias[18,24,27]. Four studies presented a serious risk of bias[21,23,25,26]. Detailed information concerning the risk of bias for each outcome is described in Figure 2.

The overall quality of evidence was moderate for the outcomes of bacteremia, cholangitis, septicemia, pancreatitis, and cholangitis in patients with suspected biliary obstruction. The quality of evidence was high for the outcomes of cholangitis in patients on intravenous antibiotic prophylaxis and mortality. Detailed information on the quality of evidence (Grading Recommendations Assessment, Development, and Evaluation) is described in Figure 3.

Outcomes

Bacteremia: Data from seven studies[20-22,24-27] were evaluated in a total of 758 patients: 371 in the intervention group and 378 in the control group. The intervention group presented a bacteremia rate of less than 7% with a statistical difference compared to the control group (RD = -0.07, 95%CI: -0.14 to -0.01, P = 0.03) (Figure 4A).

Cholangitis: Analysis of nine studies[18-23,25-27], totaling 1658 patients (794 in the intervention group and 864 in the control group) showed no significant differences between the groups (RD = -0.02, 95%CI: -0.05 to 0.02, P = 0.32) (Figure 4B).

Septicemia: Septicemia was evaluated in seven studies[19-22,24,25,27], totaling 1152 patients (568 assigned to the intervention group and 584 to the control group) and showed no significant differences between the groups (RD = -0.02, 95%CI: -0.06 to 0.01, P = 0.18) (Figure 4C).

Pancreatitis: Pancreatitis was evaluated in five studies[18,21-23,26], totaling 798 patients (371 assigned to the intervention group and 427 to the control group) and showed no significant differences between the groups (RD = -0.02, 95%CI: -0.06 to 0.01, P = 0.19) (Figure 4D).

Cholangitis in patients with suspected biliary obstruction: Data from three studies[18,19,26] were evaluated in a total of 838 patients (302 assigned to the intervention group and 536 to the control group) and showed no significant difference between the groups (RD = 0.02, 95%CI: -0.08 to 0.13, P = 0.66) (Figure 5A).

Cholangitis in patients on intravenous antibiotic prophylaxis: Analysis of eight studies[18-22,24,26,27], totaling 1540 patients (755 assigned to the intervention group and 785 to the control group) showed no significant difference between the groups (RD = -0.02, 95%CI: -0.05 to 0.01, P = 0.25) (Figure 5B).

Mortality: Mortality rate was evaluated in nine studies[18-22,24-27], totaling 1638 patients (804 of the intervention group and 834 of the control group) and showed no significant difference between the groups (RD = 0.00, 95%CI: -0.01 to 0.01, P = 0.71) (Figure 4E).

DISCUSSION

We analyzed 10 RCTs to assess whether antibiotic prophylaxis positively impacts patients undergoing elective ERCP, thus preventing complications after the procedure. Including a total of 1757 patients, this meta-analysis showed no statistical difference in the rates of cholangitis, septicemia, pancreatitis, and mortality. However, our study showed a lower bacteremia rate in the antibiotic group.

Although our systematic review and meta-analysis revealed less risk of bacteremia in the group that underwent antibiotic prophylaxis, there are doubts about whether this finding has any clinical relevance. Antibiotics are highly prescribed drugs in clinical practice. It is estimated that about 50% of antibiotic use in hospitals (both outpatient and inpatient) is not appropriately prescribed[28]. A meta-analysis published in 2009, which evaluated ERCP-induced cholangitis as an outcome, showed that antibiotics do not prevent cholangitis[29]. However, another meta-analysis from 2010 showed that prophylactic antibiotics could reduce bacteremia rates and may prevent cholangitis in patients undergoing elective ERCP[30]. Nonetheless, due to conflicting findings in the literature, it is not possible to state that reducing bacteremia rates leads to less cholangitis. Another critical point is that the

Table 1 Characteristics of included studies

Ref.	Year	Type of study	Intervention	Participants	Bacteremia	Cholangitis	Pancreatitis	Septicemia	Mortality
Brandes *et al* [23]	1981	RCT	Minocycline 300 mg orally	Total: 118 Antibiotics: 39 Control: 79	N/A	Intervention: 0/39 Control: 1/79	Intervention: 1/39 Control: 2/79	N/A	N/A
Sauter *et al* [22]	1990	RCT	Cefotaxime 2 g IV, 15 min before ERCP	Total: 100 Antibiotics: 50 Control: 50	Intervention: 1/50 Control: 8/50	Intervention: 1/50 Control: 2/50	Intervention: 0/50 Control: 0/50	Intervention: 0/50 Control: 0/50	Intervention: 0/50 Control: 0/50
Niederau *et al*[21]	1994	RCT	Cefotaxime 2 g IV. 15 min before ERCP	Total: 100 Antibiotics: 50 Control: 50	Intervention: 0/50 Control: 4/50	Intervention: 0/50 Control: 4/50	Intervention: 2/50 Control: 3/50	Intervention: 0/50 Control: 8/50	Intervention: 0/50 Control: 0/50
Byl *et al*[20]	1995	RCT	Piperacillin, 4 g IV, 3/d	Total: 68 Antibiotics: 34 Control: 34	Intervention: 0/30 Control: 7/32	Intervention: 2/34 Control: 10/34	N/A	Intervention: 0/30 Control: 5/32	Intervention: 0/34 Control: 5/34
Finkelstein *et al*[27]	1996	RCT	Cefonicid 1 g IV, 1 h before ERCP	Total: 179 Antibiotics: 88 Control: 91	Intervention: 3/88 Control: 2/91	Intervention: 7/88 Control: 2/91	N/A	Intervention: 0/88 Control: 0/91	Intervention: 0/88 Control: 0/91
Lorenz *et al* [24]	1996	RCT	Cefuroxime 1.5 g IV, 30 min before ERCP	Total: 99 Antibiotics: 49 Control: 50	Intervention: 3/49 Control: 8/50	N/A	N/A	Intervention: 3/49 Control: 5/50	Intervention: 0/49 Control: 0/50
van den Hazel *et al* [19]	1996	RCT	Piperacillin 4 g IV, 30 min before ERCP	Total: 551 Antibiotics: 270 Control: 281	N/A	Intervention: 12/170 Control: 17/281	N/A	Intervention: 2/170 Control: 3/281	Intervention: 3/170 Control: 2/281
Räty *et al*[18]	2001	RCT	2g of ceftazidime IV, 30 min before ERCP	Total: 315 Antibiotics: 155 Control: 160	N/A	Intervention: 0/155 Control: 7/160	Intervention: 4/155 Control: 15/160	N/A	Intervention: 1/155 Control: 0/160
Spicak *et al* [26]	2002	RCT	Amoxicillin – clavulanic acid 2.4 g IV	Total 165 Antibiotics: 77 Control: 88	Intervention: 18/73 Control: 24/84	Intervention: 4/77 Control: 3/88	Intervention: 6/77 Control: 10/88	N/A	Intervention: 2/77 Control: 2/88
Llach *et al* [25]	2006	RCT	Clindamycin 600 mg and gentamicin 80 mg IM, 1 h before ERCP	Total: 62 Antibiotics: 31	Intervention: 2/31 Control: 2/30	Intervention: 1/31 Control: 1/31	N/A	Intervention: 0/31 Control: 0/30	Intervention: 0/31 Control: 0/30

Control: 31	

3/d: Three times a day; ERCP: Endoscopic retrograde cholangiopancreatography; IM: Intramuscular; IV: Intravenous; N/A: Not available; RCT: Randomized controlled trial.

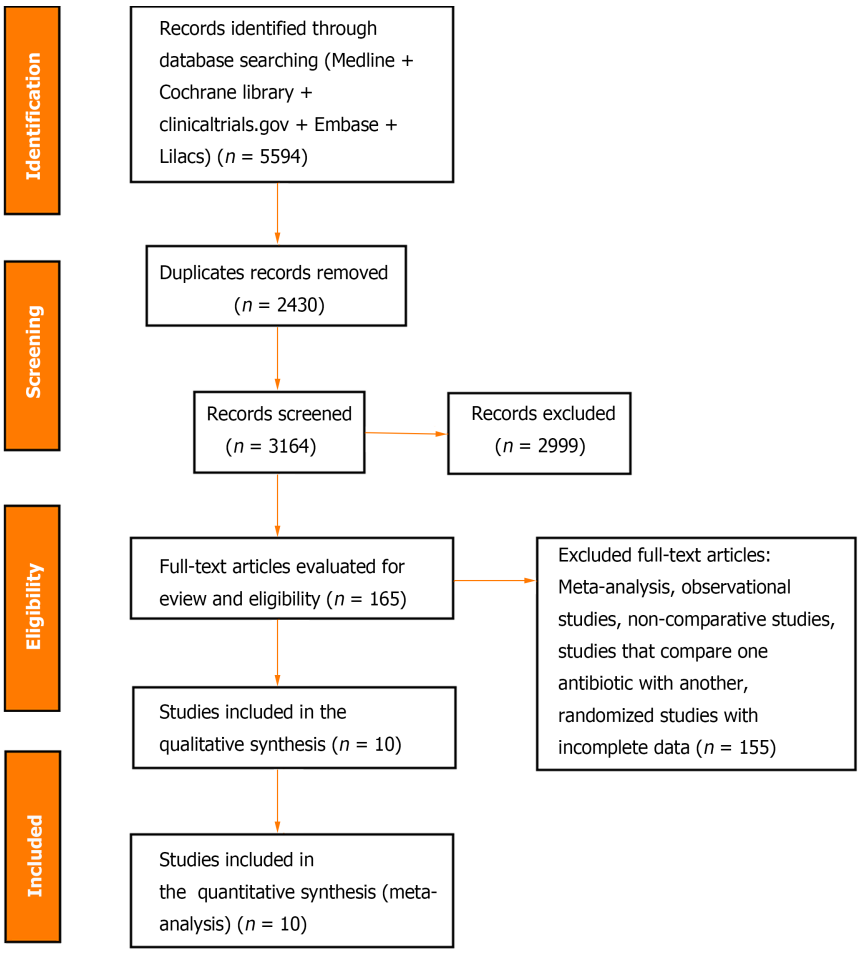

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Figure 1 Flow diagram showing the article selection process.

indiscriminate use of antibiotics has the potential to increase bacterial resistance and lead to the emergence of multiresistant germs[31]. Antimicrobial drug resistance is a global health problem that causes a high impact and inflicts an enormous economic burden worldwide. The World Health Organization reported that the ratio of morbidity and mortality rate of diseases due to the spreading of multidrug resistant strains will lead to a substantial economic loss of approximately 100 trillion US Dollars by 2050[32].

Post-ERCP cholangitis, although infrequent, is a significant concern due to its 3% mortality rate. It is mainly associated with incomplete drainage of the bile ducts, equipment contamination[8], or an immunosuppressed state[4]. Many studies[18-23,25-27] demonstrated that prophylactic antibiotics administered in patients undergoing elective ERCP do not reduce the risk of cholangitis. A prospective study that analyzed antibiotic prophylaxis in patients undergoing elective ERCP published[33] in 2014 with 138 patients who underwent this procedure showed that cholangitis was greater when incomplete biliary drainage was present. They concluded there was no benefit in using prophylactic antibiotics to reduce cholangitis and sepsis in patients with satisfactory biliary drainage. Another retrospective study published in 2008[11], with 11484 patients over 11 years to identify post-ERCP infections, was performed in patients with biliary obstruction and immunosuppression. This study showed that the higher risk of infection was in the group who underwent ERCP after liver transplantation.

Sepsis is a significant cause of morbidity and mortality worldwide[34]. Antibacterial therapy is the cornerstone treatment for infection[35], reducing the risk of septic complications and the length of stay. However, prophylactic use of antibiotic agents is not a consensus in terms of minimizing infection risk after some procedures. In ERCP, the main factor for developing clinically relevant sepsis appears to be biliary obstruction. The presumed mechanism by which obstruction leads to sepsis is increased biliary

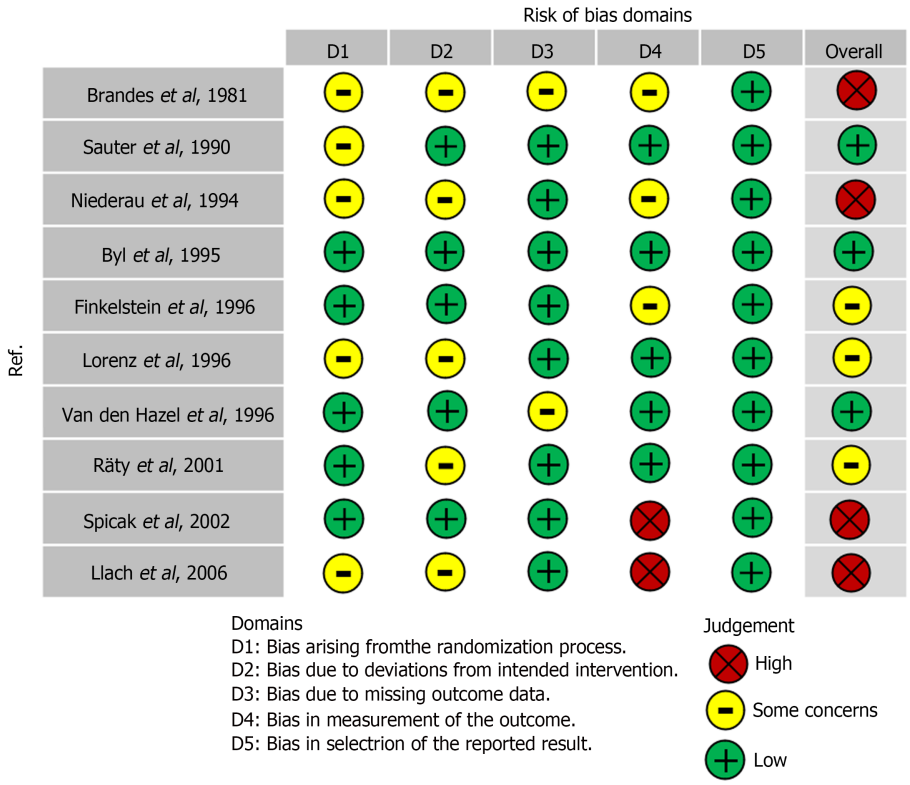

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Figure 2 Risk of bias according to the ROB-2 tool.

pressure leading to bile-venous reflux. The manner this manifests clinically depends on the content of the bile: whether it contains a contrast medium during ERCP or percutaneous transhepatic cholangiography[36]. The use of prophylactic antibiotics to prevent bacterial colonization in an unobstructed biliary system is not recommended because bacteria in the bile (bacterobilia) are clinically silent. On the other hand, using prophylactic antibiotics appears to be beneficial for patients with biliary obstruction and known or suspected bacterobilia. Antibiotics should be continued until the obstruction is relieved. In addition, antibiotic prophylaxis to prevent biliary colonization that can lead to systemic sepsis is warranted in particular circumstances of an immunocompromised patient or a patient with primary sclerosing cholangitis[37]. When analyzing specific trials of patients with suspected biliary obstruction [18,19,26], they also showed no significant effect in antibiotic prophylaxis to prevent cholangitis, especially when drainage was effective. The study published in 2007 by Thawee *et al*[38], including patients who underwent complete biliary drainage, showed that antibiotic prophylaxis did not reduce the rate of cholangitis.

Studies[18-22,24,26,27] that used the intravenous route of administration of prophylactic antibiotics found no significant differences in the incidence of cholangitis. The type of antibiotic also did not influence the prevention of infectious complications. It should be noted that many classes of antibiotics were used, so it is not possible to determine which of them may be indicated for antibiotic prophylaxis. Besides, it is important to study the best antibiotic regimen and dosage when indicated, which is still not clear in the current literature.

In the present study, there was no significant difference in the incidence of pancreatitis in patients undergoing ERCP. The most recent study[39] from 2015 demonstrated that antibiotic prophylaxis did not influence the rate of pancreatitis in patients with risk factors such as choledocholithiasis, primary sclerosing cholangitis, and incomplete biliary drainage.

Also, there was no significant difference between the intervention and control groups regarding mortality. In general, mortality rates in the analyzed studies were low. The deaths were related to bleeding from percutaneous transhepatic drainage, cholangitis, severe sepsis, and pancreatic cancer.

Despite this being the largest study on the subject and included only RCTs, our study was not exempt from limitations. Some of the included studies[21,23,25,26] presented a high risk of bias. Also, in some studies[27], some high-risk groups (patients with incomplete biliary drainage) were not excluded when analyzing the results of cholangitis and sepsis. The absence of a homogeneous antibiotic regimen protocol and standardized methods to assess bacterial resistance may also limit the interpretation of the results. Also, the studies included in this meta-analysis are not recent, but this could be explained because during our literature search we found randomized studies that did not reach the estimated sample size of patients and thus were not included for this reason. Others are still under development.

Antibiotic treatment compared to non-antibiotic in patients undergoing ERCP eletive
Bibliography:

Certainty assessment							Summary of findings				
Participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95%CI)	Anticipated absolute effects	
							With non-antibiotic	With antibiotic treatment		Risk with non-antibiotic	Risk difference with antibiotic treatment
Bacteremia											
758 (7 Rictos)	Serious[1]	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ Moderate	55/387 (14.2%)	27/371 (7.3%)	**RR 0.50** (0.23 to 1.08)	142 per 1.000	**70 more per 1.000** (from 10 more to 140 more)
Cholangitis											
1658 (9 RCTs)	Serious[1]	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ Moderate	47/864 (5.4%)	28/794 (3.5%)	**RR 0.69** (0.32 to 1.49)	54 per 1.000	**17 fewer per 1.000** (from 37 fewer to 27 more)
Septicemia											
1152 (7 RCTs)	Not serious	Serious[2]	Not serious	Not serious	None	⊕⊕⊕◯ Moderate	21/584 (3.6%)	5/568 (0.9%)	**RR 0.35** (0.11 to 1.11)	36 per 1.000	**20 more per 1.000** (from 10 fewer to 60 more)
Pancreatitis											
798 (5 RCTs)	Serious[1]	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ Moderate	30/427 (7.0%)	13/371 (3.5%)	**RR 0.51** (0.27 to 0.97)	70 per 1.000	**20 more per 1.000** (from 10 fewer to 60 more)
Suspected biliary obstruction											
838 (3 RCTs)	Not serious	Serious[2]	Not serious	Not serious	None	⊕⊕⊕◯ Moderate	27/536 (5.0%)	16/302 (5.3%)	**RR 1.05** (0.18 to 6.14)	50 per 1.000	**20 fewer per 1.000** (from 130 fewer to 80 more)
Effect of intravenous antibiotics on post-ERCP cholangitis											
1540 (8 RCTs)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	46/785 (5.9%)	27/755 (3.6%)	**RR 0.64** (0.28 to 1.45)	59 per 1.000	**20 more per 1.000** (from 10 fewer to 50 more)
Mortality											
1638 (9 RCTs)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	4/834 (0.5%)	4/804 (0.5%)	**RR 1.19** (0.30 to 4.73)	5 per 1.000	**0 fewer per 1.000** (from 10 fewer to 10 more)

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Figure 3 Quality of evidence assessed by Grading Recommendations Assessment, Development, and Evaluation. [1]There was risk of bias in selection of the reported result according to ROB-2; [2]High heterogeneity. CI: Confidence interval; ERCP: Endoscopic retrograde cholangiopancreatography; RCT: Randomized controlled trials; RR: Risk ratio.

However, for our systematic review and meta-analysis, we relied on current clinical guidelines with recommendations on the use of antibiotic prophylaxis as well as references from recent prospective clinical studies that also analyzed its use.

Overall, antibiotic prophylaxis for ERCP reduces the rate of bacteremia without affecting other complications. Bacteremia is defined as the presence of bacteria in the bloodstream[40]. Among hospitalized patients, the incidence of bacteremia is highest within a few days of admission and varies according to clinical and patient characteristics[41]. Bacteremia related to endoscopic procedures can result in local infections due to contamination of "sterile" bile ducts by an endoscopic accessory and contrast material[42]. Patients undergoing ERCP may develop infectious complications depending on their comorbidities, especially in those in whom immunity is compromised and in patients with incomplete biliary drainage. In these patients, the use of prophylactic antibiotics is recommended. Appropriate use of antibiotics will reduce hospitalization time, health care costs, and the risk of mortality. On the other hand, the indiscriminate and inappropriate use of antibiotics is of concern, and bacterial resistance has become an increasing challenge. Also, the profile of procedure-related pathogens has evolved in recent years and multidrug resistant organisms have been reported[42]. Therefore, appropriate and timely selection of empiric antimicrobial treatment has become difficult. The clinical relevance and bacterial resistance should be weighed before routinely using antibiotic prophylaxis for ERCP. Considering the findings of our meta-analysis and in agreement with previous studies[29,30], the recommendation to not use antibiotic prophylaxis is maintained.

CONCLUSION

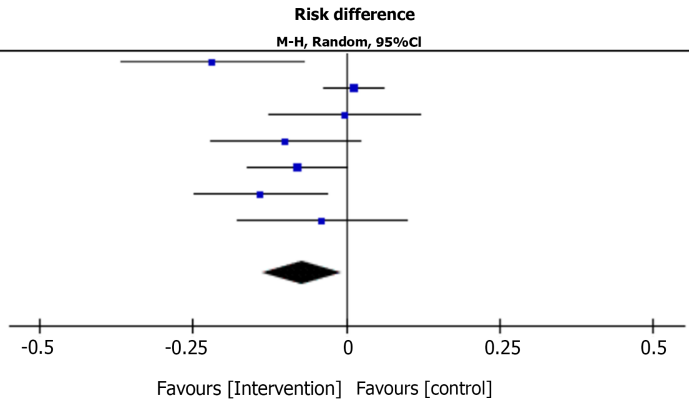
Prophylactic antibiotics reduce the rate of bacteremia in patients undergoing elective ERCP. However, its use does not have an impact on other associated complications such as cholangitis, septicemia, pancreatitis, and mortality.

A

Study or subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk difference M-H, Random, 95%CI
BYL b, 1995	0	30	7	32	10.5%	-0.22 [-0.37, -0.07]
Finkelstein R, 1996	3	88	2	91	0.21%	-0.01 [-0.04, 0.06]
Llach J, 2006	2	31	2	30	12.7%	-0.00 [-0.13, 0.12]
Lorenz R, 1996	3	49	8	50	12.9%	-0.10 [-0.22, -0.02]
Niederau C, 1994	0	50	4	50	17.2%	-0.08 [-0.16, 0.00]
Sauter G, 1990	1	50	8	50	14.3%	-0.14 [-0.25, -0.03]
Spicak J, 2002	18	73	24	84	11.4%	-0.04 [-0.18, 0.10]
Total 95% (CI)		371		387	100.0%	-0.07 [-0.14, -0.01]
Total events	27		55			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 17.20$, df = 6 ($P = 0.009$); $I^2 = 65\%$

Test for overall effect: Z = 2.17 ($P = 0.03$)

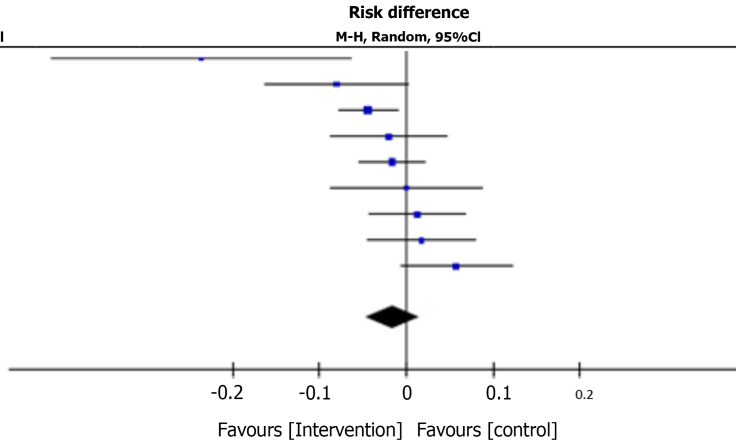


B

Study or subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk difference M-H, Random, 95%CI
BYL b, 1995	2	34	10	34	2.8%	-0.24 [-0.41, -0.06]
Niederau C, 1994	0	50	4	50	8.6%	-0.08 [-0.16, 0.00]
Räty S, 2001	0	155	7	160	17.4%	-0.04 [-0.08, -0.01]
Sauter G, 1990	1	50	2	50	10.9%	-0.02 [-0.09, 0.05]
van den Hazel SJ, 1996	12	270	17	281	16.6%	-0.02 [-0.05, 0.02]
Llach J, 2006	1	31	1	31	7.9%	0.00 [-0.09, 0.09]
Brandes JW, 1981	1	39	1	79	12.9%	0.01 [-0.04, 0.07]
Spicak J, 2002	4	77	3	88	11.6%	0.02 [-0.04, 0.08]
Finkelstein R, 1996	7	88	2	91	11.3%	0.06 [-0.01, 0.12]
Total 95% (CI)		794		864	100.0%	-0.02 [-0.05, 0.02]
Total events	28		47			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 18.63$, df = 8 ($P = 0.02$); $I^2 = 57\%$

Test for overall effect: Z = 0.99 ($P = 0.32$)

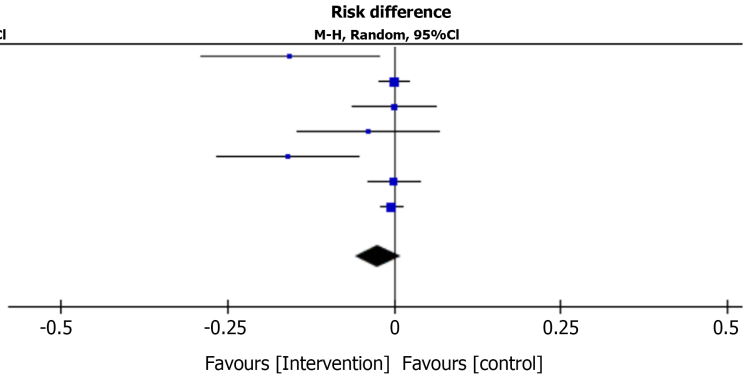


C

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk difference M-H, Random, 95%CI
Byl B, 1995	0	30	5	32	5.2%	-0.16 [-0.29, -0.02]
Finkelstein R, 1996	0	88	0	91	22.8%	0.00 [-0.02, 0.02]
Llach J, 2006	0	31	0	30	14.0%	0.00 [-0.06, 0.06]
Lorenz R, 1996	3	49	5	50	7.4%	-0.04 [-0.15, 0.07]
Niederau C, 1994	0	50	8	50	7.5%	-0.16 [-0.27, -0.05]
Sauter G, 1990	0	50	0	50	19.2%	0.00 [-0.04, 0.04]
van den Hazel SJ, 1996	2	270	3	281	23.8%	-0.00 [-0.02, 0.01]
Total 95% (CI)		568		584	100.0%	-0.02 [-0.06, 0.01]
Total events	5		21			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 27.23$, df = 6 ($P = 0.0001$); $I^2 = 78\%$

Test for overall effect: Z = 1.35 ($P = 0.18$)

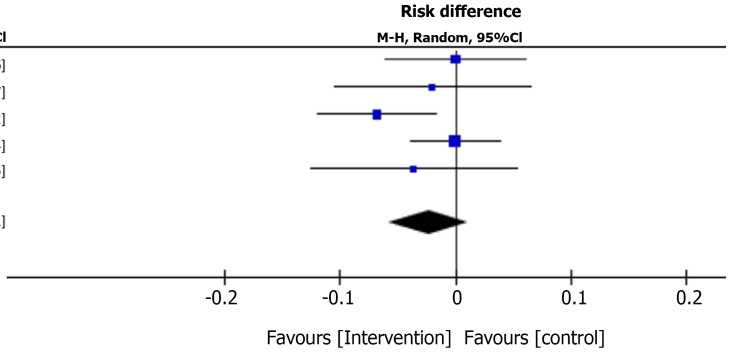


D

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk difference M-H, Random, 95%CI
Brandes JW, 1981	1	39	2	79	20.1%	0.00 [-0.06, 0.06]
Niederau C, 1994	2	50	3	50	12.5%	-0.02 [-0.11, 0.07]
Räty S, 2001	4	155	15	160	24.1%	-0.07 [-0.12, -0.02]
Sauter G, 1990	0	50	0	50	31.7%	0.00 [-0.04, 0.04]
Spickan J, 2002	6	77	10	88	11.6%	-0.04 [-0.13, 0.05]
Total 95% (CI)		371		427	100.0%	-0.02 [-0.06, 0.01]
Total events	13		30			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.65$, df = 4 ($P = 0.16$); $I^2 = 40\%$

Test for overall effect: Z = 1.30 ($P = 0.19$)



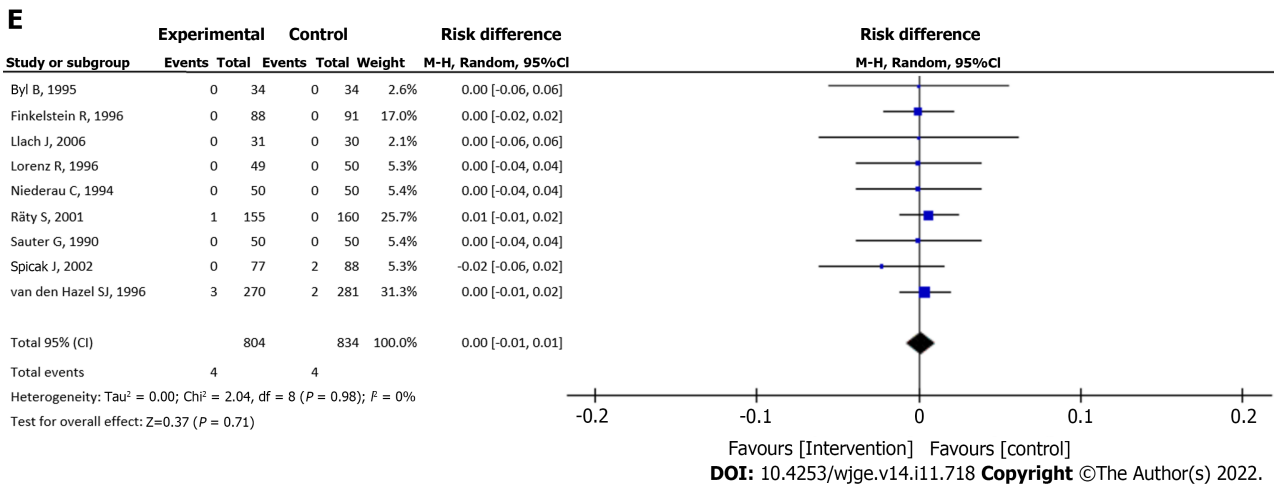


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Figure 4 Forrest plot studies reporting the rate of bacteremia (A), cholangitis (B), septicemia (C), pancreatitis (D), and mortality (E). CI: Confidence interval.

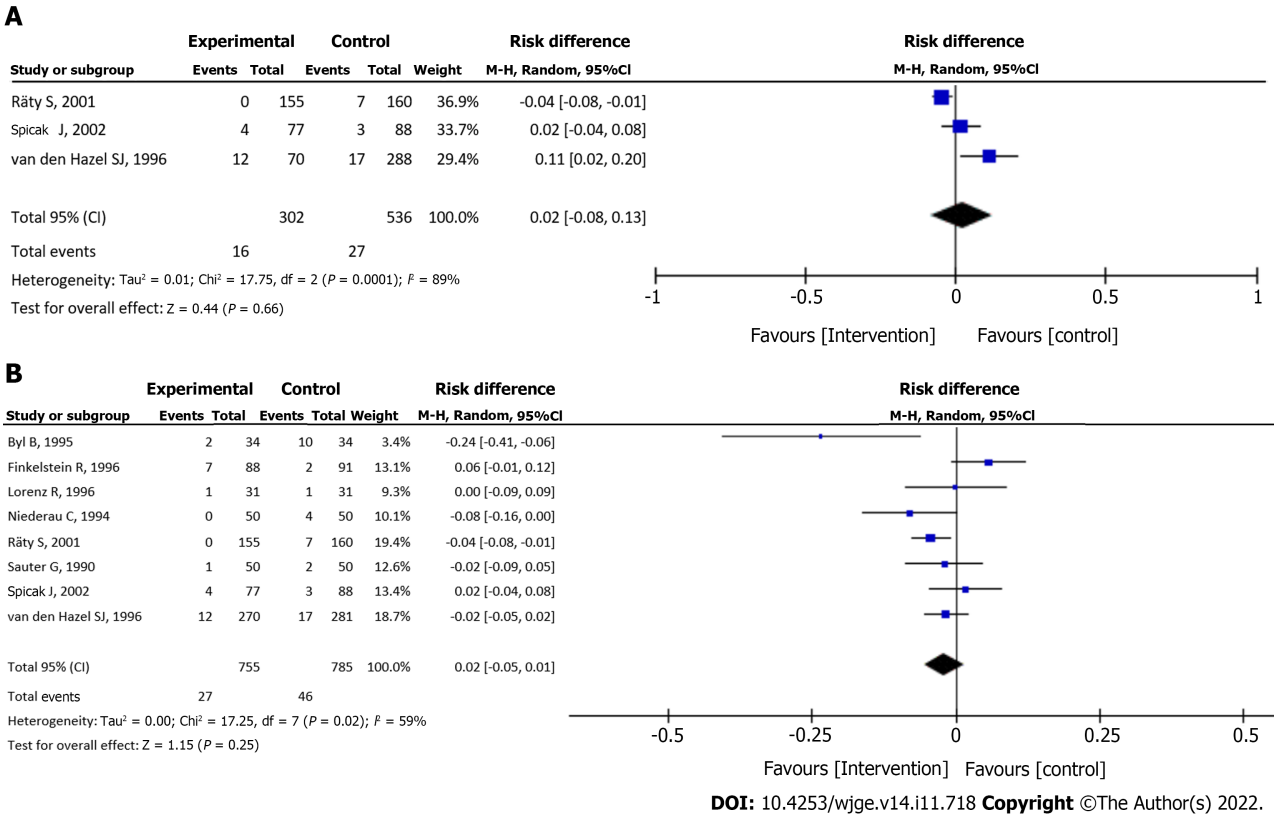

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Figure 5 Forrest plot studies reporting the rate of cholangitis in patients with suspected biliary obstruction (A) and on intravenous antibiotic prophylaxis (B). CI: Confidence interval.

ARTICLE HIGHLIGHTS

Research background

The prophylactic use of antibiotics in endoscopic retrograde cholangiopancreatography (ERCP) is controversial. The most common adverse events include bacteremia, cholangitis, and pancreatitis. Although recent guidelines regarding antibiotic prophylaxis for ERCP do not recommend its routine use, the data to support this recommendation is not robust.

Research motivation

Antimicrobial drug resistance is a global health problem that causes a high impact and inflicts an

enormous economic burden worldwide. The World Health Organization reported that the ratio of morbidity and the mortality rate of diseases due to the spreading of multidrug resistant strains will lead to a substantial economic loss by 2050. Due to the lack of data in the literature, we performed a systematic review and meta-analysis to evaluate whether antibiotic prophylaxis impacts the rate of complications related to elective ERCP.

Research objectives

This systematic review and meta-analysis aimed to assess whether antibiotic prophylaxis reduced the rates of complications such as bacteremia, cholangitis, sepsis, pancreatitis, and mortality in patients undergoing elective ERCP.

Research methods

This systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. A comprehensive search of multiple electronic databases was performed only including randomized controlled trials.

Research results

Ten randomized clinical trials with a total of 1757 patients that compared the use of antibiotic and non-antibiotic prophylaxis in patients undergoing elective ERCP were included. There was no significant difference between groups regarding the incidence of cholangitis [risk difference (RD) = -0.02, 95% confidence interval (CI): -0.05 to 0.02, P = 0.32], cholangitis in patients with suspected biliary obstruction (RD = 0.02, 95%CI: -0.08 to 0.13, P = 0.66), cholangitis on intravenous antibiotic prophylaxis (RD = -0.02, 95%CI: -0.05 to 0.01, P = 0.25), septicemia (RD = -0.02, 95%CI: -0.06 to 0.01, P = 0.25), pancreatitis (RD = -0.02, 95%CI: -0.06 to 0.01, P = 0.19), and all-cause mortality (RD = 0.00, 95%CI: -0.01 to 0.01, P = 0.71). However, the antibiotic prophylaxis group presented a 7% risk reduction in the incidence of bacteremia (RD= -0.07, 95%CI: -0.14 to -0.01, P = 0.03).

Research conclusions

Considering our findings, antibiotic prophylaxis in patients undergoing elective ERCP reduces the risk of bacteremia. Still, it does not appear to impact the rate of other adverse events.

Research perspectives

Antibiotics are highly prescribed drugs in clinical practice, but they can have adverse effects. Larger randomized controlled trials regarding the use of prophylactic antibiotics on ERCP in specific populations of patients are still warranted.

FOOTNOTES

Author contributions: Merchan MFS contributed to acquisition of data, analysis, interpretation of data, drafting the article, revising the article, and final approval; de Moura DTH, de Oliveira GHP, Proença IM, Monte ES, Ide E, and Moll CF contributed to analysis and interpretation of data and revising the article; Sánchez-Luna SA contributed to interpretation of data, drafting the article, revising the article, and final approval; Bernardo WM contributed to analysis of data, interpretation of data, drafting the article, revising the article, and final approval; de Moura EGH contributed to analysis and interpretation of data, drafting the article, revising the article, and final approval.

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LETTER TO THE EDITOR

Minimally invasive colorectal surgery learning curve

Serafino Vanella, Enrico Coppola Bottazzi, Giancarlo Farese, Rosa Murano, Adele Noviello, Tommaso Palma, Maria Godas, Francesco Crafa

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Abstract

The learning curve in minimally invasive colorectal surgery is a constant subject of discussion in the literature. Discordant data likely reflects the varying degrees of each surgeon's experience in colorectal, laparoscopic or robotic surgery. Several factors are necessary for a successful minimally invasive colorectal surgery training program, including: Compliance with oncological outcomes; dissection along the embryological planes; constant presence of an expert tutor; periodic discussion of the morbidity and mortality rate; and creation of a dedicated, expert team.

Key Words: Learning curve; Colorectal surgery; Laparoscopy; Robotic surgery; Minimally invasive surgery; Cusum method

Core Tip: Minimally invasive techniques, such as laparoscopy and robotic surgery, are increasingly used in the treatment of colorectal cancer. The learning curve for minimally invasive surgery is not well-defined and subject to several influences. A successful operation depends on the preparation of the surgical team to imagine and contemplate the specific details for each step. The principal objective of treating the pathologic condition through the appropriate extent of resection must be clearly defined.

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TO THE EDITOR

We read with interest the article of Perivoliotis *et al*[1] regarding the change point analysis of the learning curve (LC) in laparoscopic colorectal surgery. Hermann Ebbinghaus[2], in 1885, and Theodore Paul Wright[3], in 1936, introduced the term "learning curve" to express the average learning rate for a procedure for the aviation industry. This term is now used extensively, including in laparoscopic colorectal surgery. Proficiency is obtained when predefined variables reach a plateau and results are comparable with those in the literature[4,5]. Multiple parameters define proficiency in laparoscopic colorectal surgery, but the total number of cases required to complete the LC and obtain proficiency is not conclusively known[6-11]. Current reports vary between 11 cases to 152 cases[6,9,11-13].

The LC process from learning to competence to mastery has been analyzed by the cumulative summation method. This method does not require a large sample size or grouping. Therefore, it is very practical and precise[14,15]. Reports have shown that the surgeon's experience correlates significantly with the safety and feasibility of laparoscopic colorectal surgery. Case selection is another factor that affects the LC because it has not yet been standardized during training[7].

Oncologic efficacy of the laparoscopic colorectal procedure is a crucial parameter in the assessment of learning. This goal is measured by negative surgical distal and circumferential margins and an adequate number of harvested lymph nodes. However, oncologic efficacy should not be compromised and inappropriate resection is not justified regardless of the stage of the training period[6]. The use of well-structured and standardized intra- and perioperative protocols ensures that all patients can benefit from the advantages of minimally invasive surgery[16-19].

We agree with the authors that a specialized team dedicated to colorectal surgery is important. This team must be composed of surgeons, anesthetists, pathologists and nurses and must be supported by specialists with high levels of expertise in colorectal surgery from the diagnostic step to the perioperative period to the follow-up.

The site of colorectal surgery also has an effect on the LC. We would like to emphasize the difference between the LC of colonic surgery and the LC of rectal surgery, particularly the low rectum. Rectal cancer surgery underwent a major breakthrough with the introduction of the circular stapler in the 1970s that facilitated lower anastomoses[20]. This revolutionary tool has greatly facilitated the preservation of the sphincter. In 1988, Heald[21] described the "holy plane" of rectal surgery, which lead to the realization of the importance of tumor-free circumferential margins. Understanding of the fundamental role of total mesorectal excision (TME) in cancer success has steadily grown to become the standard approach for rectal cancer treatment. It has been 30 years since the introduction of the concepts of TME and tumor-free circumferential resection margins. Numerous surgical technological advances have developed over these three decades, improving the ability to perform surgeries with less invasive measures[22].

Adequate margin resection and specific postoperative morbidity (anastomotic leakage) are critical issues in the care of patients with lower rectal cancer. Morbidity following large bowel anastomosis can impact the hospital course of patients undergoing colon resection. Additionally, anastomotic morbidity is quite often influenced by the distance of the suture line from the anal verge. The double-stapled technique is one of the commonly used methods to construct low colorectal or coloanal anastomosis after low anterior resection of rectal cancer[23].

Anastomotic leak ranges from less than 1% to approximately 25%[24]. It is associated with serious short-term morbidity and mortality and long-term functional compromise. It may also have a negative impact on the oncologic outcomes of colorectal cancer[25,26]. Multiple stapler firings, low tumor location, longer operation time, perioperative blood transfusion and male sex were the most common risk factors of anastomotic leak after the double-stapled technique. Different methods have been devised to improve the outcome of the double-stapled technique, including elimination of dog-ears using sutures, transanal reinforcement of anastomosis, single-stapled transanal transection, transanal pull-through with single-stapling technique, natural orifice intracorporeal anastomosis with extraction of specimen procedure, hand-sewn colonic J pouch and vertical division of the rectum[22,25].

Transanal visual inspection obtained through endoscopy or self-retaining anal retractors may be the only reliable means to assure bowel transection at a proper distance from the distal tumor margin. In 2015, we proposed an original technique of low colorectal anastomosis with transanal control after TME with the removal of the rectal stump suture line avoiding dog-ear formations[27], as described in the TICRANT study[28]. The same technique can be applied to partial mesorectal excision and proximal colorectal anastomosis. The ability to perform low rectal anastomosis with an adequate transanal assessment of distal resection margins, technical adequacy, and transanal repair of any resulting anastomotic defects was a clinical necessity[29-32]. We continue to utilize transanal control after anastomosis fashioning with the reverse air leak test and endoscopic control with fluorescence. These controls are useful because problems can be identified early and repaired intraoperatively, thus reducing the number of complications and ostomies.

Colorectal surgery training programs should also distinguish between colonic surgery and rectal surgery as well as between surgery of the right and left colon. In accordance with what the authors wrote, complete mesocolic excision follows the principles of TME with central vascular ligation and dissection along the embryological planes[33].

Over the past 30 years, there have been tremendous innovations in minimally invasive colorectal surgery with countless new technologies and approaches[34,35]. Numerous studies have confirmed that laparoscopic surgery is equal to or superior to open surgery. Further studies have focused on single incision, transluminal endoscopic surgery of the natural orifice and most recently on robotic surgery[36, 37]. The comparison between the LCs of laparoscopic and robotic colorectal surgery is still under investigation.

A shorter LC in robotic colorectal surgery compared to laparoscopic surgery has been reported. A plateau has been reached after 15-25 cases[12,38]. This is likely due to reducing the differences between laparoscopy and robotics. In our center, we use a robotic approach in colorectal and low rectal cancer surgery. Robotic surgery appears to be less invasive due to three-dimensional vision and better visualization of the anatomical structures; the EndoWrist® (Intuitive, Sunnyvale, CA, United States) allows accurate movements in confined spaces and other intrinsic characteristics of the robotic platform[13,39-42].

For experienced laparoscopists, the LC of robotic surgery seems to be shorter[43]. Flynn *et al*[44] showed that operating times for robotic surgery might be faster than laparoscopy when surgeons are inexperienced with both platforms. This may be related to a superior baseline performance rather than a shorter LC. A selection of the most suitable patients can help surgeons in the early stages of training. A small primary tumor, no previous adjuvant chemoradiotherapy, appropriate body mass index, and few medical comorbidities are ideal characteristics for robotic surgery[45].

In the early stages of learning there are still many difficulties, despite the numerous advantages of the da Vinci robot: Preoperative times are longer; the freedom of movement of the robotic arms during the operation is limited by the relatively fixed angle and position; and the lack of force feedback from the robotic arm, which limits the sensitivity of the operator who must judge the effect of pulling and cutting by sight[46-49]. Of note, the rates of disease-free survival and overall survival on a small sample size were similar for robotic and laparoscopic surgery[50].

All innovative techniques with clinical advantages will also have disadvantages when compared to established methods. The key is continued refinement and modification by masters of the craft. More extensive comparative studies are needed to give definitive conclusions regarding the LC in minimally invasive colorectal surgery. Regardless of the approach used, dissection along the embryological planes, correct knowledge of the anatomical and vascularization variants, respect for oncological outcomes, regular tutoring, variation of the surgical approach based on the results, and a dedicated team are essential prerequisites for a colorectal surgery training program.

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CORRECTION

Correction to "Laparoscopy-assisted resection of colorectal cancer with situs inversus totalis: A case report and literature review"

Wei Chen, Jing-Lin Liang, Jun-Wen Ye, Yan-Xin Luo, Mei-Jin Huang

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Abstract

Correction to "Laparoscopy-assisted resection of colorectal cancer with situs inversus totalis: A case report and literature review" *World J Gastrointest Endosc* 2020; 12: 310-316. In this article, we have replaced the previous TNM stage of colorectal cancer (T4aN0M0) and the revised TNM stage is provided (T4a-N1cM1c).

Key Words: Colorectal cancer; Situs inversus totalis; Hyperthermic intraperitoneal chemotherapy; Case report; Correction

Core Tip: This is a correction to "Laparoscopy-assisted resection of colorectal cancer with situs inversus totalis: A case report and literature review" *World J Gastrointest Endosc* 2020; 12: 310-316. In this article, the previous TNM stage of colorectal cancer is T4aN0M0, which has been replaced by the revised TNM stage (T4aN1cM1c).

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TO THE EDITOR

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Correction to "Laparoscopy-assisted resection of colorectal cancer with situs inversus totalis: A case report and literature review"[1]"(ID: Manuscript NO. 77875, Correction). Those comments are all valuable and very helpful for our paper.

The previous TNM stage of colorectal cancer is T4aN0M0, which has been replaced by the revised TNM stage (T4aN1cM1c). Since the specific number of versions of tumor staging was not indicated in our previous text, the staging of the tumor was different from the latest one. Therefore, we would like to modify the postoperative staging of tumors, which should be T4aN1cM1c.

FOOTNOTES

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OPINION REVIEW

Role of multidetector computed tomography angiography in non-variceal upper gastrointestinal bleeding: A comprehensive review

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Abstract

Non-variceal upper gastrointestinal bleeding (NVUGIB) is a common gastroenterological emergency associated with significant morbidity and mortality. Upper gastrointestinal endoscopy is currently recommended as the gold standard modality for both diagnosis and treatment, with computed tomography traditionally playing a limited role in the diagnosis of acute NVUGIB. Following the introduction of multidetector computed tomography (MDCT), this modality is emerging as a promising tool in the diagnosis of NVUGIB. However, to date, evidence concerning the role of MDCT in the NVUGIB diagnosis is still lacking. The aim of our study was to review the current evidence concerning the role of MDCT in the diagnosis of acute NVUGIB.

Key Words: Gastrointestinal bleeding; Upper gastrointestinal bleeding; Non-variceal upper gastrointestinal bleeding; Computed tomography; Multidetector computed tomography; Multidetector computed tomography angiography

Core Tip: Upper gastrointestinal endoscopy is currently recommended as the first-line technique for diagnosis and treatment of non-variceal upper gastrointestinal bleeding (NVUGIB). Conversely, computed tomography has a limited role in the diagnosis of acute NVUGIB. However, following the introduction of multidetector computed tomography (MDCT), this modality is emerging as a promising tool in the diagnosis of NVUGIB. Nevertheless, to date, evidence concerning the role of MDCT in the NVUGIB diagnosis is still lacking. Our study aimed to review the current evidence concerning the role of MDCT in the diagnosis of acute NVUGIB.

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INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is the most common gastroenterological emergency with an annual incidence of 40-150/100000 population[1-3]. It is defined as hemorrhage occurring from a source located proximal to the ligament of Treitz. Based on the etiology, it is usually classified as variceal and non-variceal upper gastrointestinal bleeding (NVUGIB), with peptic ulcers, neoplasms and Mallory-Weiss syndrome being the most common causes of NVUGIB[1,2,4].

Despite marked advances in the management of acute UGIB, its mortality rate is still high ranging from 8% to 14%[5-7], and increasing up to 40% in high-risk patients[8].

Following hemodynamic stabilization, esophagogastroduodenoscopy (EGD) is currently recommended as the first-line diagnostic procedure in NVUGIB patients, allowing for simultaneous localization, characterization and hemostatic treatment in the majority of bleeding lesions[9-11]. The reported EGD sensitivity and specificity for UGIB are 92%-98% and 30%-100%, respectively[3]. However, EGD often fails to identify the exact bleeding site in case of massive UGIB (> 1 mL/min), being non-diagnostic in 10% of cases of UGIB[3,12]. Furthermore, Vreeburg *et al*[13] reported unsuccessful diagnosis at first endoscopy in 24% of acute UGIB patients, with endoscopic view impairment for excessive blood or clots in 15% of cases.

As opposed to acute lower gastrointestinal bleeding[14-16], computed tomography (CT) has currently a limited role in the diagnosis of acute UGIB and its routine adoption in the setting of acute NVUGIB is not recommended[9-11]. However, the introduction of multidetector CT (MDCT) technology has led to increased image resolution and markedly decreased scanning time, thus allowing the identification of contrast medium (CM) extravasation into the bowel lumen before contrast medium dilution. Furthermore, the ability of helical CT to detect active gastrointestinal bleeding may exceed the lower limit of 0.5 mL/min reported for mesenteric angiography and may approach the 0.2 mL/min limit of 99mTc-red blood cell scintigraphy[17]. Thus, recently, MDCT has been increasingly adopted in the diagnostic approach of most vascular diseases, and a promising role of this technique in the NVUGIB diagnosis has been suggested[18,19]. Anyway, evidence regarding the value of MDCT in NVUGIB is still limited. The aim of our study was to extensively review the current evidence with regard to the role of MDCT in the diagnosis of acute NVUGIB.

LITERATURE SEARCH

We performed a comprehensive literature search of the PubMed (MEDLINE) and EMBASE electronic databases up to July 2022, in order to identify relevant studies evaluating the role of MDCT in the diagnosis of acute NVUGIB. The medical search strategy used the terms "computed tomography", "CT", "computed tomography angiography", "CTA", "multidetector computed tomography", "MDCT", "non-variceal upper gastrointestinal bleeding", and "non-variceal upper gastrointestinal haemorrhage" in various combinations, using the Boolean operators AND, OR, and NOT. Search strategy was limited to human studies and articles written in English. Meeting abstracts, individual case reports, case series (< 5 cases), review articles, position papers, editorials, commentaries, and book chapters were excluded from our review. The reference lists of pertinent identified studies and related review articles were carefully hand-searched in order to obtain any additional eligible studies.

ROLE OF MDCT IN NVUGIB

Evidence

A total of 9 studies were included in our final analysis[20-28]. All but 3 prospective studies[20,24,25] were retrospective[21-23,26-28]. With the exception of one study comparing enhanced and unenhanced MDCT[26], in all of the remnant studies intravenous contrast-enhanced MDCT scan with at least an arterial phase acquisition was evaluated[20-25,27,28]. No CM was orally administered in any of the included studies. Main characteristics of the included studies in which MDCT was adopted in the diagnosis of acute NVUGIB are summarized in Table 1. Figures 1-3 show three cases of severe NVUGIB in which MDCT was performed immediately after EGD, providing bleeding etiology identification and thus guiding further treatment.

In 2006, Yoon *et al*[20] first prospectively evaluated the role of arterial phase MDCT in 7 patients admitted for acute massive NVUGIB in whom endoscopic examination or hemostasis failed. A high accuracy of MDCT for the detection and localization of the bleeding sites was showed.

Later on, in a small retrospective case series MDCT was able to detect the bleeding source in all cases and to identify the bleeding etiology in 9 out of 10 cases. Of note, CT provided a diagnosis in 6 patients after negative findings at angiography (n = 2) and endoscopy (n = 4). In the remaining 4 patients, CT was the initial imaging method providing a diagnosis in all 4, and no further diagnostic work-up was performed. Moreover, CM extravasation was detected in all patients with acute severe NVUGIB (7/10) and the identified NVUGIB etiology mainly included rare causes of massive NVUGIB (aortoduodenal fistula, n = 4 and arterial pseudoaneurysm, n = 4, and arteriobiliary fistula, n = 1), requiring non-endoscopic treatment[21].

In 2008, Jaeckle *et al*[22] retrospectively reported the efficacy of MDCT in 10 UGIB patients in whom upper endoscopy failed to reveal the bleeding source. In 9 out of 10 patients MDCT was able to localize the bleeding site, while active bleeding was showed in 5 cases. In the only false-negative finding, angiographic and endoscopic follow-up revealed duodenal invasion of a small pancreatic carcinoma with duodenal bleeding.

Later on, a high MDCT accuracy for the detection of acute UGIB was reported in a small retrospective case series. Of note, MDCT criteria for acute GIB not only included the identification of active CM extravasation within bowel lumen, but also the detection of mass or pathologic vessel[23].

Subsequently, a small prospective study from Italy reported an excellent sensitivity of MDCT in identifying bleeding site and etiology (100.0% and 90.9%, respectively, compared with 72.7% and 54.5%, respectively, of endoscopy). Of note, patients in whom bleeding stopped after the operative endoscopy were not included in the study, whereas EGD failure was observed in 5 out of 11 of the included patients[24].

In 2012, Sun *et al*[25] prospectively evaluated the role of tri-phasic MDCT as the initial diagnostic investigation in patients with both severe and mild acute UGIB. As similarly previously reported, criteria for positive CT were not limited to the presence of active CM extravasation within bowel lumen, but also included identification of abnormal bowel mucosal enhancement, vascular malformation, abnormally enhancing polyp or diverticulum, or tumor. MDCT was shown to be a highly accurate first-line screening modality for both detection and localization of UGIB, effectively guiding further management. However, interestingly, no CM extravasation was observed in any of the included patients with mild UGIB[25].

Subsequently, the usefulness of MDCT prior to urgent endoscopy was confirmed in a similar large retrospective study. Indeed, pre-operative MDCT showed a diagnostic accuracy for the bleeding origin detection of 57.8% (130 of 227 patients) and 19.4% (20 of 103 patients) for the enhanced and unenhanced MDCT groups, respectively, among expert radiologists. To be mentioned, the authors excluded from their study patients in whom other therapeutic modalities, such as angiography or surgery, were performed rather than urgent endoscopy due to MDCT results. Finally, the average time needed for endoscopic detection of bleeding origin in the MDCT-positive group was significantly faster (88.1 s) than that in the MDCT-negative group (155.8 s) among patients who underwent the enhanced MDCT scan ($P \leq 0.05$)[26].

Conversely, a recent large retrospective study showed that MDCT prior to endoscopy has a significantly low sensitivity for the identification of UGIB site and etiology, as compared with endoscopy. However, of note, the study did not include cases in whom EGD failed, or the endoscopic diagnosis was other than ulcer, varices, or cancer. Moreover, unstable patients were also excluded. As stated by the authors, all of the included patients were affected by mild UGIB, thus massive and rare and causes of acute UGIB were excluded from this study[27].

Intriguingly, Jono *et al*[28] compared CT findings with two well validated clinical scores to predict mortality, rebleeding and need for endoscopic therapy in NVUGIB patients. In all patients CT was performed prior to upper endoscopy. Although upper gastrointestinal (UGI) hemorrhage and UGI wall findings on CT scan were not significant in predicting mortality and rebleeding, the first CT finding better predicted the need for endoscopic therapy than both clinical Rockall score (adjusted odds ratio 10.10) and Glasgow Blatchford score (adjusted odds ratio 10.70)[28].

Table 1 Summary of studies reporting on the role of multidetector computed tomography in the diagnosis of acute Non-variceal upper gastrointestinal bleeding

Ref.	Study design	Patients, *n*	Type of CT	Inclusion criteria	Exclusion criteria	Criteria for positive CT	Reference standard	Study aim	Results
Yoon *et al*[20], 2006	P	7	4-MDCT	Patients with massive UGIB in whom endoscopic examination or hemostasis failed	-	Active GIB: Extravasation of CM with attenuation> 90 HU within bowel lumen	Angiography	Accuracy of MDCT for detection and localization of acute massive UGIB	GIB detection: TP: 4/7, FN: 2/7, FP: 1/7, TN: 0/7, GIB localization: TP: 7/7
Scheffel *et al*[21], 2007	R	10	4-, 16-, or 64-MDCT	Patients with UGIB who underwent CT in the acute phase of hemorrhage	-	Acute GIB: Active extravasation of CM within bowel lumen; or extravasated CM with attenuation > 90 HU	Surgery, angiography, endoscopy, or pathology	Ability of MDCT to identify source and etiology of acute UGIB	GIB detection: 10/10; GIB etiology identification: 9/10
Jaeckle *et al*[22], 2008	R	10	16- or 40-MDCT	Patients with UGIB in whom endoscopic examination failed to identify the bleeding source	Serum creatinine > 250 μmol/L; or iodinated CM allergy	Active GIB: Active extravasation of CM with attenuation > 90 HU within bowel lumen; or collection of hyperdense intraluminal blood with attenuation > 90 HU	Endoscopy, angiography and/or surgery	Accuracy of MDCT for detection and localization of acute UGIB	GIB detection: TP: 9/10; FN: 1/10; GIB localization: TP: 9/10; FN: 1/10
Fung *et al*[23], 2008	R	6	64-MDCT	Patients with UGIB who underwent angiography	-	Acute GIB: Mass, abnormal vessel, or active extravasation of CM within bowel lumen	Angiography	Accuracy of MDCT for detection of acute UGIB	TP: 6/6
Frattaroli *et al*[24], 2009	P	11 (1 VUGIB)	16-MDCT	Patients with severe acute UGIB following endoscopy	Hemodynamicinstability; non-severe, intermittent, or chronic GIB; or effective endoscopic hemosthasis	Acute GIB: Active extravasation of CM within bowel lumen	Endoscopy, angiography, surgery, or post-mortem findings	Ability of MDCT to identify UGIB site and etiology	GIB site identification: Sensitivity 100% (*vs* 72.7% of endoscopy); GIB etiology identification: Sensitivity 90.9% (*vs* 54.5% of endoscopy)
Sun *et al* [25], 2012	P	33	16-, 64-, or dual-source MDCT	Patients with acute UGIB who underwent; MDCT as the initial diagnostic examination	Iodinated CM allergy; pregnancy; or serum creatinine > 2.0 mg/dL	Active GIB: Active extravasation of CM with attenuation > 90 HU within bowel lumen; focal or segmental abnormal bowel mucosal enhancement; presence of a vascular malformation; polyp or diverticulum with abnormal enhancement; or tumor	Endoscopy, angiography, surgery, or pathology	Accuracy of MDCT for detection of active UGIB	TP: 25/33; FN: 3/33; TN: 5/33
Miyaoka *et al*[26],	R	330	64-MDCT	Patients with acute UGIB	Patients who underwent other therapeutic	Active GIB: Extravasation of	Endoscopy	Accuracy of MDCT for	Enhanced MDCT: 57.8%

2014				who underwent MDCT prior to urgent endoscopy	modalities rather than urgent endoscopy due to MDCT findings	CM within bowel lumen; possible bleeding: Wall thickening; focal wall enhancement; masses, varices, and aneurysms, with or without the intraluminal high-attenuation substance		detection of acute UGIB origin	(130/227); unenhanced MDCT: 19.4% (20/103)
Jono *et al* [28], 2019	R	386	16- or 64-MDCT	Patients with NVUGIB who underwent MDCT prior to urgent endoscopy	VUGIB; or no CT exam	UGI hemorrhage: Yes or no; UGI wall change: Concavity or hypertrophy	Endoscopy	OR of risks scores based on clinical data and CT findings for predicting mortality, rebleeding and need for endoscopic therapy in NVUGIB	UGI hemorrhage: Not significant in predicting mortality and rebleeding, but significant in predicting need for endoscopic therapy (OR 10.1 for RS and 10.70 for GBS); UGI wall change: Not significant in predicting mortality, rebleeding and need for endoscopic therapy
Kim *et al* [27], 2022	R	269 (53 VUGIB)	64-MDCT	Patients with acute UGIB who underwent MDCT prior to endoscopy	Execution of endoscopy 24 h after admission; endoscopic examination failure; LGIB; acute or chronic kidney injure; or iodinated CM allergy	Active bleeding: Active extravasation of CM within bowel lumen; recent bleeding: Hemorrhagic content, suspicious hematoma, and blood clots	Endoscopy	Accuracy of MDCT for identification of status, location, and etiology of UGIB	Bleeding status identification: 32.9% (active bleeding); 27.4% (recent bleeding); 94.8% (no bleeding); bleeding location identification: 60.9% (esophagus), 60.6% (stomach), 50.9% (duodenum); bleeding etiology identification: 58.3% (ulcerative bleeding), 65.9% (cancerous bleeding), 56.6% (variceal bleeding)

CT: Computed tomography; MDCT: Multidetector-row computed tomography; UGIB: Upper gastrointestinal bleeding; GIB: Gastrointestinal bleeding; CM: Contrast medium; HU: Hounsfield units; TP: True positive; FN: False negative; FP: False positive; TN: True negative; VUGIB: Variceal upper gastrointestinal bleeding; UGI: Upper gastrointestinal; OR: Odds ratio; RS: Rockall score; GBS: Glasgow-Blatchford score; LGIB: Lower gastrointestinal bleeding.

CONCLUSION

EGD is currently recommended as the first-line modality for both diagnosis and treatment of NVUGIB, with MDCT playing only a limited role in the diagnosis of NVUGIB[9-11]. However, endoscopy may fail to identify the source of UGIB, especially in case of massive hemorrhage. Furthermore, although rare, various unusual cause of UGIB may not be properly diagnosed by endoscopy and require solely endovascular or surgical treatment[29-31]. MDCT has been suggested to be a promising non-invasive, fast and widely available diagnostic tool in the diagnosis of NVUGIB, with reported high diagnostic accuracy for both detection and localization of bleeding, especially among patients with severe hemorrhage[32]. Moreover, MDCT is capable to identify the bleeding etiology, representing the gold standard diagnostic modality for most of the unusual causes of NVUGIB. Finally, as opposed to endoscopy, MDCT is capable to accurately evaluate the bleeding lesion, providing information to extraluminal abnormalities, feeding and draining vessels, and its anatomical relationship to

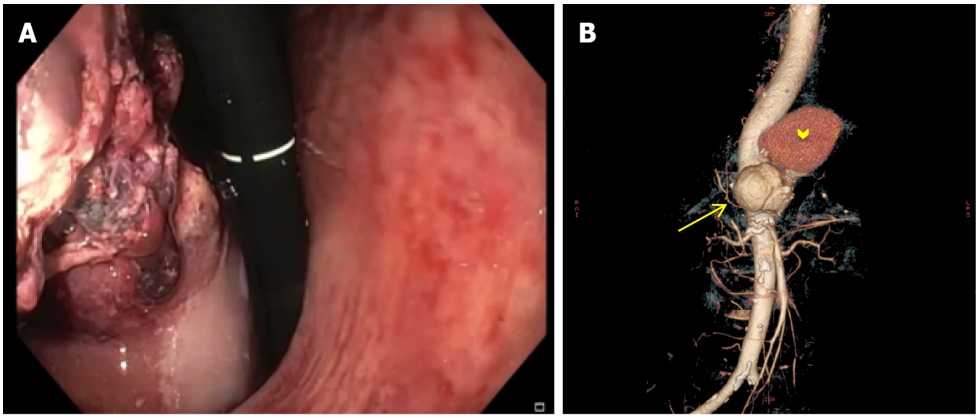

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Figure 1 Severe non-variceal upper gastrointestinal bleeding due to primary aorto-gastric fistula. A: Retroflexed endoscopic view showing gastric bulging mass partially covered by blood clots, originating from the fundus and extending to the posterior wall of the proximal body; B: Three-dimensional computed tomography angiography showing ruptured thoracoabdominal aortic aneurysm (arrow), retained by a periaortic hematoma (arrowhead).

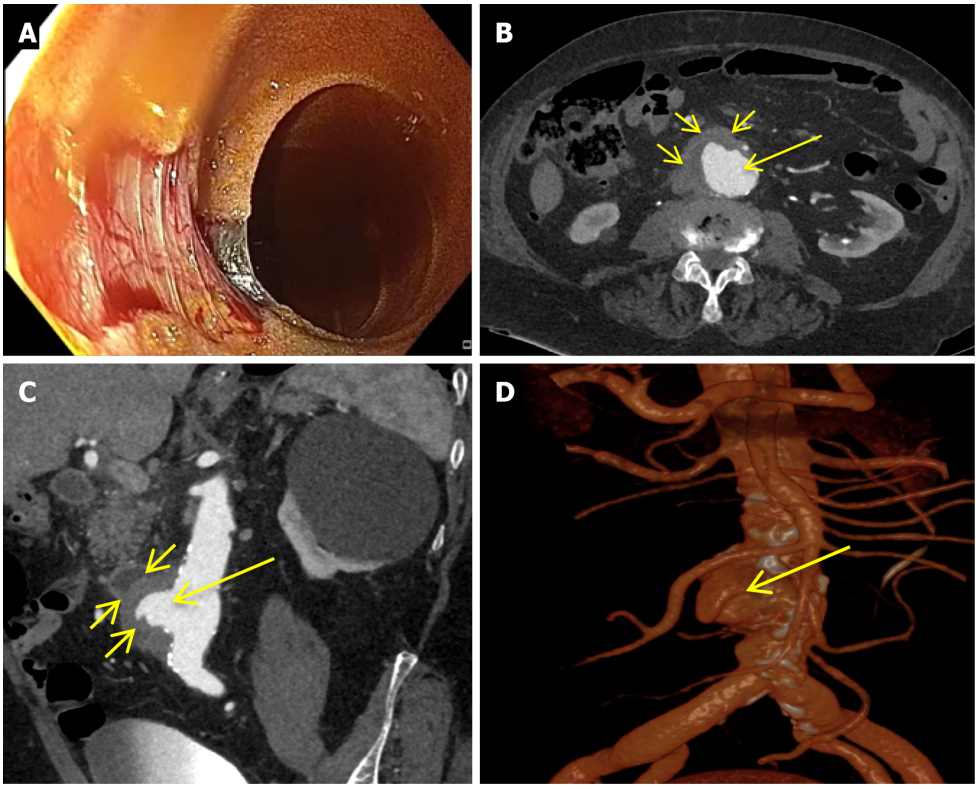

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Figure 2 Severe non-variceal upper gastrointestinal bleeding due to primary aorto-duodenal fistula. A: Esophagogastroduodenoscopy showing a large pulsating wall defect of the third duodenal portion; B-D: Axial computed tomography artery phase (B), coronal-oblique maximum intensity projection artery phase (C) and three-dimensional volume rendering reconstruction (D) showing a large outpouching from the right anterolateral wall of the abdominal aorta (B-D; long arrow) at the level of the third duodenal portion with loss of interface fat plane (B and C; short arrows), in the absence of neither air bubble within the aortic lumen and wall nor contrast medium extravasation into the duodenal lumen.

surrounding structures. Thus, MDCT has the potential to stratify patients who need earlier treatment and to assist clinicians in planning further safe, effective and tailored treatment, whether it is endoscopic, endovascular, and/or surgical.

In our opinion, MDCT angiography plays a primary role in NVUGIB patients in whom endoscopic examination fails to identify and/or to properly treat the bleeding lesion. Furthermore, in case of uncertain etiologic diagnosis at endoscopy, MDCT should be performed before treatment. Finally, across referral centers, MDCT angiography may play a role as first-line diagnostic modality in NVUGIB, especially among patients admitted for severe bleeding. Indeed, it may easily identify the bleeding

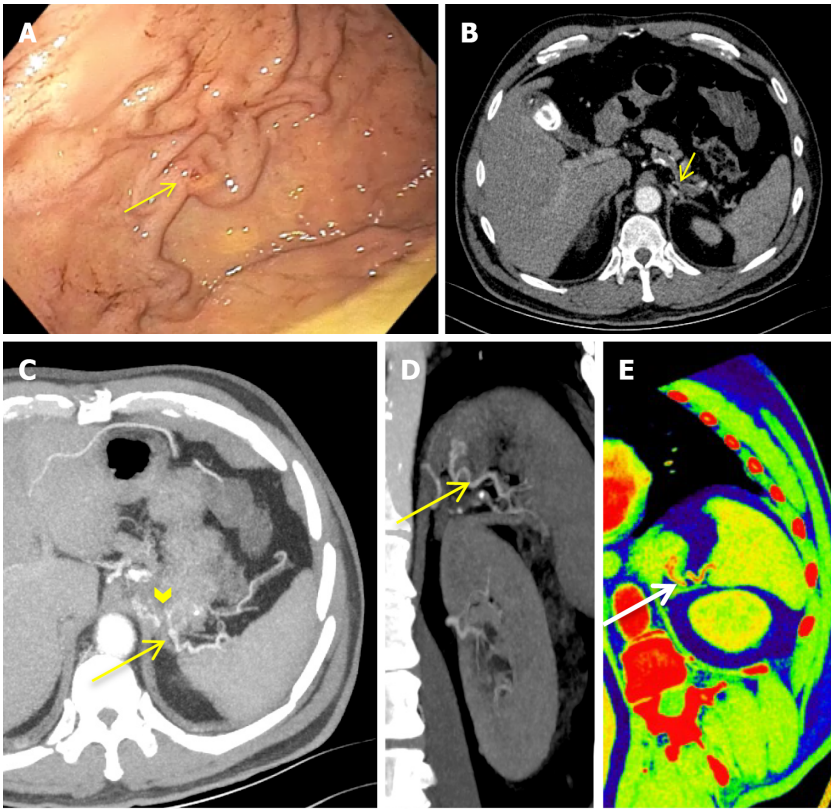

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Figure 3 Severe non variceal upper gastrointestinal bleeding due to gastric submucosal arterial collaterals secondary to splenic artery thrombosis. A: Retroflexed endoscopic view of the gastric fundus showing varicose-shaped submucosal vessels with a small erosion (arrow); B-E: Axial computed tomography dual-energy arterial phase (B) with maximum intensity projection artery phase reconstruction on axial (C) and coronal (D) multiplanar view and oblique-coronal colorimetric low keV (E) showing splenic artery thrombosis (B: short arrow) with an arterial cluster at the gastric fundus (C: arrowhead) arising from splenic artery collateral vessels (C-E: long arrow).

status, addressing the timing of treatment, and provide an etiological diagnosis of the bleeding lesion, thereby strictly directing further safe and effective management. Finally, in case of failure of endoscopic hemosthasis, emergent endovascular or surgical treatment could be directly, safely and effectively performed by the pre-alerted interventional radiologist or surgeon. However, further large prospective studies in high-volume referral centers are needed to clarify the role of MDCT in NVUGIB, especially as first-line diagnostic tool in patients affected by severe acute NVUGIB. High morbidity and mortality still associated with acute NVUGIB justify active research in this field.

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FOOTNOTES

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Endoscopic ultrasound-guided diagnosis and treatment of gastric varices

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Abstract

Gastric varices (GV) represent a common and severe complication in patients with portal hypertension, commonly seen in patients with cirrhosis and severe pancreatic disease. Endoscopic ultrasonography is a safe and efficacious approach that can perform real-time ultrasonic scanning and intervention for the gastrointestinal submucosa, portal vein and its tributaries, and collateral circulations during direct endoscopic observation. Recently, various studies have been published about endoscopic ultrasound (EUS)-guided management of GV, mainly including diagnosis, treatment, and prognostic analysis. This article reviews published articles and guidelines to present the development process and current management of EUS-guided GV procedures.

Key Words: Endoscopic ultrasound; Diagnosis; Treatment; Gastric varices

Core Tip: Gastric varices (GV) are a common and severe complication in patients with portal hypertension, and GV bleed more severely with a higher mortality rate than esophageal varices. With increased applications in GV management, endoscopic ultrasound (EUS) has demonstrated diagnosis and treatment benefits, particularly in cases of refractory bleeding or those unsuitable for conventional therapies by preoperative assessments, and thus enriches originally-limited options. The advantages of EUS exist throughout the process, from diagnosis, preoperative assessment, treatment, and efficacy evaluation to follow-up in GV patients. This article reviews published articles and guidelines to present the recent EUS-guided management of GV.

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INTRODUCTION

Gastric varices (GV) represent complex and heterogeneous collections of vascular shunts between the portal splenic venous system and systemic veins in the abdomen and chest[1]. GV are a common and severe complication in patients with portal hypertension (PH). Patients with chronic liver and pancreatic diseases are at risk of developing PH. Compared with esophageal varices (EV), GV bleed in significantly fewer patients but more severely with a higher mortality rate[2]. Despite decades of advances in diagnosing and treating procedures, managing GV bleeding in patients with PH remains a unique clinical challenge. Accurately detecting PH and GV are critical in managing PH[3]. However, conventional gastroscopy cannot effectively observe small GV and portal vein (PV) and their tributaries, not to mention its disability for real-time venous blood flow visualization during and after endoscopic procedures. Meanwhile, effective treatment options for GV bleeding used to be limited. Even in patients undergoing emergency endoscopic treatment such as emergency ligation, rebleeding and mortality rates are still non-negligible[4]. With increased applications in GV management[5-7], endoscopic ultrasound (EUS) has demonstrated diagnostic and therapeutical benefits and enriches originally-limited options. By comprehensively performing an electronic literature search of Medline/PubMed, Embase, *Reference Citation Analysis* (*RCA*) databases, and Web of Science databases from inception to September 10, 2022, we review published articles and guidelines to present the development process and current management of EUS-guided GV procedures.

CLASSIFICATION

Varied endoscopic classifications exist for GV[8], among which Sarin classification is the most commonly used. According to Sarin classification, GV exist in four types, including isolated GV type 1 (IGV1), IGV2, gastroesophageal varices type 1 (GOV1), and GOV2. The Sarin classification was based on the location of GV and their relationship with EV[2], while another one, the Hashizome classification, focuses on the form, location, and color of GV[9]. Even though few EUS-based GV classifications have been reported, esophagogastric varices were once investigated and classified into three types according to the vascular structures and locations, including the esophageal type, esophagogastric type, and solitary gastric type[10]. Another research in patients with cirrhosis proposed a new classification criterion for GV, which included three types of GV sizes and gastric wall abnormalities, respectively[11].

EPIDEMIOLOGY

According to anatomic location, GV are classified as gastroesophageal or isolated GV, and the reported incidence of GV varies in patients with PH (2%-70%)[12]. The most common GV type is the lesser curve varix, which is also classified as type 1 GOV (GOV1, Sarin classification)[2]. GV makes up about 10%-20% of all types of varices[2,13]. Previous studies have demonstrated that GV bleeding could happen at lower portal pressures when compared to esophageal varices[14,15], and the cumulative risk for GV bleeding in patients with PH at 1, 3, and 5 years has been reported to be as high as 16%, 36%, and 44%, respectively[16]. Acute GV bleeding is one of the leading causes of death in cirrhotic patients, even in patients who have undergone N-butyl-cyanoacrylate (NBC) injections. A retrospective study of 132 patients documented a 16.7% mortality rate within 6 wk after NBC injection treatment[17]. Left-sided PH (LSPH) accounts for approximately 5% of extrahepatic PH cases and is characterized by isolated GV [18]. In patients with LSPH due to pancreatic disease, GV bleeding has been reported in approximately 8% to 15% of patients[19,20].

DIAGNOSIS

EUS combines ultrasound imaging and traditional endoscopy to obtain real-time ultrasound images and provide detailed information about the gastrointestinal tract and the surrounding organs and vessels. EUS technology has enabled endoscopists to break through the observing limitation inside the digestive tract and greatly enriched the diagnosis and differential diagnosis of GV. The combination of EUS with

color or flow Doppler techniques facilitates better identification and monitoring of GV.

Accurate identification

EUS and mini-probes have played a revolutionary part in GV identification. High-frequency mini-probes can increase the sensitivity in identifying the minimal or initial varices and thus are beneficial for early diagnosis of esophageal varices and GV[21]. EUS could assess both the intraluminal and extraluminal varices in cirrhotic patients and therefore improve the management of PH[22]. Linear or radial EUS should be recommended to distinguish GV from other causes of prominent gastric folds, especially in cases with no evidence of PH or cirrhosis, as reported in patients with gastrointestinal stromal tumor or mucosa-associated lymphoid tissue lymphoma[23,24]. PH and splenic vein thrombosis remain the leading causes of GV bleeding. Accurate identification of PH is essential in managing patients with cirrhosis and pancreatic disease and preventing complications, including gastrointestinal bleeding. The endoscopic diagnosis of PH by conventional gastroscopy is mainly based on the visualization of bluish dilated tortuous varices, while GOV are not present in approximately 60% of patients with PH[25]. GV is located in a deeper submucosa than EV and is, therefore, difficult to differentiate from other causes of prominent gastric folds by conventional endoscopy. However, even blood flow in small varices not diagnosed by gastroscopy can be visualized by color Doppler endoscopic ultrasonography (CD-EUS), and the minimum diameter of varices detected was 2 mm in the 1990s[26]. Real-time portal pressures and liver biopsies can be acquired during one EUS procedure, so EUS has recently become increasingly popular in patients suspected of having PH or liver cirrhosis[27]. Therefore, EUS is a practical approach for differentiating PH from other related diseases.

Preprocedural evaluation

Predictors of GV bleeding include fundal varices, large varices (> 5 mm), red color signs, and Child-Pugh C class[28]. EUS can determine the bleeding risk of GV patients and facilitate timely therapeutic intervention for high-risk patients without active bleeding. EUS and high-frequency mini-probes can accurately measure the variceal radius and wall thickness, which supports subsequent identification of patients at risk for variceal bleeding[29,30]. In addition, estimating the presence of GV in patients with massive active gastrointestinal bleeding is distressing, while CD-EUS can help better confirm GV, determine accessibility, and select a suitable treatment plan in these cases. CD-EUS and EUS-guided angiography can also assess the primary feeding vein system of GV, fluid dynamics, and gastrorenal shunts[31,32], which is of great significance for the subsequent treatment selection and the reduction of postoperative complications. More importantly, EUS-guided evaluation is a reproducible and non-invasive approach.

Therapeutic evaluation

EUS procedures have been proven effective in assessing GV obliteration and identifying perforated veins, thus improving real-time monitoring and repeated injection management[5,8,33]. A prospective cohort study of 102 patients concluded that red signs, variceal size, and presence of para-gastric veins indicated a high risk of GV rebleeding after endoscopic therapy, all of which were identifiable by EUS [34]. EUS can visualize the altered ultrasonic echo immediately during endoscopic treatments, and the disappearance of the original blood flow verified by CD-EUS was thought to be one indicator of real-time therapeutic efficacy[26]. Meanwhile, alterations of variceal radius and wall thickness assessed by EUS also predicted endoscopic and pharmacological efficacy[30]. CD-EUS allows assessments of vascular blood flow and possible morphologic or hemodynamic changes after endoscopic treatment. A prospective observational study of 30 patients demonstrated that feeder vessels of GV could be identified during endoscopic procedures, and GV would disappear immediately after targeted injections of these feeding vessels[35]. Furthermore, follow-up EUS after obliteration helps to identify the remaining flow in the perforating vein and decide whether to repeat endoscopic procedures to reduce the possibility of postoperative bleeding[36]. Previous studies have demonstrated severe peri-EV and large perforating EV detected by a 20 MHz mini-probe as valuable indicators for EV recurrence after endoscopic injection sclerotherapy[37]; in addition, biweekly EUS monitoring could identify requirements for repeated NBC injection and decrease recurrent bleeding rates (18.5% *vs* 44.7%, P = 0.0053) in cirrhotic patients with bleeding GV[5]. Precise obliteration assessment of targeted GV contributes to reducing injection doses and related fatal embolization, which is a way safer and more objective than traditional estimation only by GV "hardening" after injection.

Treatment

Interventional EUS procedures have undergone tremendous development over the past three decades. EUS technology has evolved rapidly from a diagnostic tool to a promising therapeutic modality in patients with GV. Acute GV bleeding in patients with PH is a severe medical emergency, and the immediate therapeutic goals are to control bleeding, prevent early recurrence (within 5 d), and reduce 6-wk mortality[38,39]. Direct endoscopic cyanoacrylate injection is recommended as the first-line therapy for GV bleeding. Meanwhile, other injection procedures with the aid of EUS are increasingly performed due to their safety, efficiency, and accuracy[31]. EUS-guided injection procedures in GV patients

included EUS-glue, EUS-coil, EUS-coil & glue, EUS-thrombin, EUS-coil & thrombin, and EUS-coil & gelatin[5,7,31,40]. Previous studies have reported that EUS-guided injection has a significantly lower rebleeding rate (8.8% *vs* 23.7%, $P = 0.045$) and requires a smaller amount of cyanoacrylate (2.0 ± 0.8 mL *vs* 3.3 ± 1.3 mL, $P < 0.001$) compared to direct injection in a randomized controlled trial[41]. A meta-analysis of 851 GV patients in 23 studies revealed that EUS-guided GV procedures demonstrated superior clinical efficacy than conventional endoscopic glue injection in obliteration, recurrence, and long-term rebleeding, which increasingly emphasizes the advantages of EUS-guided procedures in GV [42].

EUS-guided sclerotherapy

Endoscopic sclerotherapy has been reported effective in treating bleeding varices and preventing the first variceal bleeding[43]. However, endoscopic sclerotherapy demonstrated less effectiveness in GV than in EV. Commonly used sclerosants include ethanolamine oleate (EO), glucose solutions, sodium tetradecyl, and acetic acid[44]. Larger injection doses are contemplated to avoid reduced efficacy caused by the early flush of injected sclerosants, but massive sclerosant injections may cause serious complications such as gastric necrosis and perforation[45]. In a prospective study of 92 consecutive, nonrandomized patients with variceal bleeding, it was concluded that endoscopic sclerotherapy only demonstrated temporary control of GV bleeding, and the high incidence of severe early rebleeding required alternative treatments or modified sclerotherapy techniques[46]. Balloon-occluded endoscopic sclerotherapy has been demonstrated as an effective and safe prophylactic treatment for high-risk GV with significantly reduced sclerotherapy volume in a prospective, randomized, comparative clinical trial, and this procedure can even be used in patients without gastrorenal shunts[47]. In contrast, EUS-guided sclerotherapy can offer a real-time observation during GV injection and reduce sclerosant dosage as well as complications by accurately injecting an appropriate amount of sclerosant into the target location. Meanwhile, EUS-guided sclerotherapy showed a lower recurrence rate and more extended recurrence than conventional sclerotherapy in a randomized controlled trial of 50 patients with cirrhosis and varices[48]. However, considering that the survival disadvantage from EO injection therapy was partially related to its lower hemostasis rate (55% *vs* 88%, $P = 0.023$) and higher early bleeding rates[49], experts believe that cyanoacrylate is superior to EO in treating GV bleeding.

EUS-guided tissue adhesive injection

EUS-guided tissue adhesive injection is to inject tissue adhesive into the targeted GV *via* a fine-needle aspiration (FNA) device. Three leading tissue adhesives used in endoscopic injections are NBC, 2-octyl-cyanoacrylate, and NBC plus methacryloxysulfolane[50], among which NBC is the most commonly employed agent, and it has been proved to have faster and firmer obliteration efficacy in GV than other alternatives, such as thrombin, absorbable gelatin sponge (AGS), and alcohol[51]. Endoscopic therapy with NBC is recommended for acute bleeding from IGV and those GOV2 that extend beyond the cardia [38]. Direct injection of tissue adhesives in GV patients was first reported by Soehendra *et al*[52] in 1986, which resulted in definitive hemostasis. Many years later, EUS-guided cyanoacrylate injection was reported with technical success in five GV patients[31]. Since then, numerous studies have been conducted using EUS-guided cyanoacrylate injection procedures[36,53]. EUS visualization of GV may improve hemostasis efficacy due to precise targeting and real-time obliteration confirmation while remaining less affected by blood; therefore, EUS-guided procedures seem more suitable in active bleeding with no need for gastric rinsing[54]. Even though endoscopic injection therapy has been proven minimally invasive and effective[55], these procedures with sclerosants or glue may cause severe complications occurring neither in EUS injections nor traditional injections, including systemic embolization, fever, pain, and recurrent bleeding[13,56]. Due to the potential presence of right-to-left shunts, traditional tissue adhesive injections may lead to fatal multiple systemic embolisms, so extreme caution was recommended for cyanoacrylate injection in adolescents with PH of unknown origin[57]. Therefore, reducing cyanoacrylate-related complications has always been one of the research hotspots, while the critical point of reducing complications is to minimize the injection dose effectively. Consequently, the Clip-assisted cyanoacrylate injection procedure was reported to be safe, convenient, and efficacious in treating GV with concomitant gastrorenal shunt[58], and our center has recently recorded a modified EUS-guided selective NBC injection procedure in an LSPH patient with good hemostasis efficacy and no post-operational gastrointestinal bleeding and ectopic embolism due to reduced injection dosage[59]. In addition, many details of EUS-guided injection procedures remain to be further explored, for example, 19- or 22-gauge needles have been used and reported without comparison in previous studies[36,53], and there is still no consensus on the exact EUS-guided tissue adhesive injection procedure.

EUS-guided coil embolization

EUS-guided coil embolization is to inject coils into the targeted blood vessels through EUS to interrupt the blood supply and thus achieve hemostasis. These coils are made up of light metal alloy and synthetic fibers, and they can obliterate GV with fewer embolization complications than those caused by tissue adhesive. EUS-guided coil embolization was first reported in a case report of successful hemostasis in refractory ectopic variceal bleeding[60], which provided a new idea for GV therapy. EUS-

guided coil embolization in GV patients was reported shortly thereafter[61]. In the above study, the target site for puncture and coil placement was modified from GV to its perforating feeding vein, successfully blocking blood flow and reducing the number of coils[61]. Surprisingly, a follow-up study found that EUS-guided coil embolization could achieve GV disappearance in most patients with only one endoscopic intervention[36]. Although EUS-guided coil therapy appeared superior in treating GV due to a higher technical success rate, fewer endoscopies, and a lower complication rate and reintervention rate[36,40], it remains to be determined whether the EUS-guided coil or tissue adhesive injection procedure is preferred. Coil migrating from the targeted varices and significant bleeding from the puncture site were both observed in previous studies[62,63]. Moreover, since the advantages of reduced endoscopic interventions and recurrent bleeding rates in EUS-guided coil embolization procedure comes at the expense of multiple coil placement and additional risks of radiation exposure, EUS-guided coil injection was believed to be significantly more expensive, technically more demanding, and not viable in many patients by some experts[64].

EUS-guided coil embolization combined with tissue adhesive injection

Despite EUS-guided tissue adhesive injection being reported to improve accuracy compared with conventional procedures, postprocedural ectopic embolization and other complications were still disturbing. Meanwhile, although EUS-guided coil embolization demonstrated a relatively low probability of ectopic embolism, unsatisfactory hemostasis still existed in some patients. Both these approaches have their advantages and disadvantages. Since embolizations caused by cyanoacrylate were thought to be mainly related to the injection volume, reducing the injection dose has become a key to breakthrough. Coils with attached synthetic fibers may decrease the injected glue dosage (1 mL less per patient than that in the conventional procedure), thereby reducing the incidence of ectopic embolism while achieving equal obliteration efficacy[65]. This new method combines EUS-guided tissue adhesive injection and coil embolization to achieve complementary advantages and satisfactory effectiveness. In the same study, transesophageal injection access from the distal esophagus to the fundus was first introduced and has demonstrated many benefits, including avoiding the difficulty of retroflexing the endoscope, no hindrance caused by blood in the stomach, and no disruption of the gastric mucosa overlying GV[65]. Moreover, an observational study of GV patients revealed a 100% technical success rate and 96.6% complete variceal obliteration rate in the EUS-guided coil and cyanoacrylate embolization procedure[35]. In a retrospective study of 152 patients with GV, 125 patients underwent EUS-guided combined injection of coils and cyanoacrylate glue, with a mean number of 1.4 coils (range 1-4) and 2 mL (range 0.5-6) cyanoacrylate per patient; after a mean follow-up of 436 d, only 4 (3%) patients presented with mild delayed upper GI bleeding due to coil/glue extrusion[66]. Furthermore, compared with EUS-guided coil injection alone, EUS-guided coil embolization combined with tissue adhesive injection demonstrated a higher variceal occlusion rate (86.7% *vs* 13.3%, $P < 0.001$), lower postoperative rebleeding rate (3.3% *vs* 20%, $P = 0.04$), and lower reintervention rate (16.7% *vs* 40%, $P = 0.01$)[7]. A meta-analysis of 536 patients concluded that EUS combination therapy with coil embolization and cyanoacrylate injection appeared to be preferred for GV over EUS-based monotherapy among a variety of EUS-guided therapies available due to its lower adverse event rates compared to cyanoacrylate alone (10% *vs* 21%, $P < 0.001$) and similar rates compared to coil embolization alone (10% *vs* 3%, $P = 0.057$)[67]. Although the above studies supported the superiority of EUS-guided combined injection of coils and cyanoacrylate glue over the application of coils or cyanoacrylate glue alone[7,65,66], there is still a lack of evidence of optimal coil numbers and mid-long term complications. Moreover, some experts believe that standard endoscopic cyanoacrylate injections are easier to perform and more accessible for endoscopists worldwide. In contrast, EUS-guided joint injections are more challenging and time-consuming and thus may be more beneficial for only a few selected and severe GV cases[68].

Other EUS-guided injections

Due to numerous complications after routine tissue adhesive injections[13,56,57], several studies have reported alternatives to cyanoacrylate, which included AGS, thrombin, EO. AGS is a type of purified collagen with liquefaction ability and thus appears not associated with post-injection ulcerations. EUS-guided coil embolization and AGS was reported to be a novel alternative to cyanoacrylate with high clinical success rates and low risk for complications in treating bleeding GV in a retrospective review[40,69]. Some experts have also suggested human thrombin as a simple and practical alternative to tissue adhesives due to fewer complications[70,71], but thrombin demonstrated inferior GV obliteration efficacy than cyanoacrylate. Another case series reported successful hemostatic efficacy in a follow-up period of 57 mo after EUS-guided coil deployment with sclerosant (EO). The authors believed that both isolated GV and their feeding veins would be reliably obliterated after this procedure[72]. However, most of these studies compared their EUS-guided injection procedures only with conventional cyanoacrylate injections but not with EUS-guided cyanoacrylate injections, and thus further research with more patients is still needed.

EUS-guided endovascular treatments

Transjugular intrahepatic portosystemic shunt (TIPS) has been proven effective in reducing portal

venous pressure and is especially recommended in patients with persistent variceal bleeding uncontrolled by endoscopic and medical therapy and postoperative rebleeding within 5 d[38]. Nevertheless, TIPS could increase risks for patients with congestive heart failure, pulmonary hypertension, advanced cirrhosis, or hepatic encephalopathy[73]. EUS techniques offer real-time visualizations of various vascularity without radiation exposure and promising alternatives for endovascular therapy, such as EUS-guided intrahepatic portosystemic shunt (EIPS), EUS-guided portal pressure gradient (EUS-PPG), and EUS-guided partial splenic embolization (PSE). Compared with traditional puncture of the PV branch from the hepatic vein, a technically challenging procedure with serious complications, EUS guidance can directly confirm the vascular flow after stent deployment and expansion[74]. EIPS was recommended due to the advantages of non-transjugular access and reduced vascular injuries. EUS-guided portal venography with carbon dioxide using a 25 gauge FNA needle was reported feasible, technically simple, and safe in a porcine model a decade and a half ago[75]. Two years later, EIPS creation was reported to be a valuable alternative to conventional TIPS in a live porcine model with normal PV pressure[76]. After that, EIPS with direct portal pressure measurements proved a novel alternative to TIPS in a study of five Yorkshire pigs[74]. In a pilot study that enrolled 28 patients with liver diseases, EUS-PPG procedures demonstrated promising safety, availability, and simplicity in managing patients with liver disease[77]. Recently, EUS-PPG with a 22-gauge FNA needle demonstrated accuracy and security as an alternative to hepatic venous pressure gradient mea-surements in a prospective study of 12 patients with hepatic sinusoidal obstruction syndrome or Budd-Chiari syndrome[6]. However, the major limitation of these two studies was the exclusion of patients with increased bleeding risks (patients with an international normalized ratio > 1.5 or platelet count < 50 were excluded)[6,77]. These above EUS technologies are gradually transitioning from animal models to patients. Meanwhile, EUS-guided PSE was first reported in a patient with alcoholic cirrhosis and variceal bleeding as an alternative procedure for preventing recurrent GV bleeding and hypersplenism [78]. EUS-guided coil implantation and following glue injection were performed in isolated collateral outside the gastric wall in a perigastric location to achieve vascular embolization; reduced GV was confirmed by follow-up endoscopy, and authors believed that the access to the splenic artery through the gastric wall has the advantage of a shorter puncture path[78]. Despite all these developments in EUS-guided endovascular treatments, more data are yet demanded to compare EUS-guided and radiation-guided endovascular therapies.

LIMITATIONS

Although increased utilizations have demonstrated promising benefits of EUS-guided procedures, and some experts claim them as first-line strategies[11], EUS-guided interventions are not yet one of the routine endoscopic procedures for GV patients and are just recommended after failures of conventional therapies. Meanwhile, limited EUS-based GV classifications exist, and most GV are classified by endoscopic criteria. Moreover, there is still a lack of acknowledged standards for EUS-guided procedures and their roles in primary prophylaxis, acute hemorrhage, and secondary prophylaxis in GV patients, and most studies are retrospective and nonrandomized with small numbers of GV patients. As such, limited data are available to evaluate the mid-long term efficacy and safety of various EUS-guided treatments. Further prospective randomized trials and guidelines are still needed to optimize EUS-guided procedures in GV. Furthermore, numerous treatment options exist for GV, among which EUS-guided procedures are mainly performed in tertiary care centers due to the limited availability of EUS and well-trained specialists[27]. Under such circumstances, TIPS and balloon-occlusion retrograde transvenous obliteration were still the central and practical options for salvage therapies in patients with refractory variceal bleeding. Additionally, most previous studies focused on investigating the advantages of EUS-guided procedures over traditional endoscopic ones, while direct comparisons between diverse EUS-guided approaches are still limited.

CONCLUSION

EUS-guided diagnoses and treatments have recently emerged as convenient diagnostic procedures and promising hemostatic interventions for GV (Table 1), particularly in cases of refractory bleeding or those unsuitable for conventional therapies by preoperative assessment. EUS procedures have already proved capable of effective real-time visualization, accurate identification, and perioperative assessment in GV. Meanwhile, various EUS-guided GV injection approaches and highly effective endovascular procedures, such as EUS-guided coil embolization combined with tissue adhesive injection, EIPS, and EUS-guided PSE, have demonstrated encouraging clinical outcomes and developmental potentials. These EUS-guided diagnoses and treatments are currently recommended for patients with appropriate affordability, disease severity, and collateral pathway anatomy in advanced EUS centers. Additionally, multidisciplinary discussion team recommendations could provide preferable personalized management and a remarkably reduced rebleeding risk[22].

Table 1 Endoscopic ultrasound-guided diagnosis and treatment of gastric varices

EUS application	Potential benefits	Areas of concern	Ref.
Diagnosis			
Accurate identification	Improving diagnostic sensitivity and differential diagnosis; real-time	-	[21-27]
Preprocedural evaluation	Predicting bleeding risk and determining treatment; reproducible and non-invasive	-	[29-32]
Therapeutic evaluation	Improving real-time monitoring and repeated injection management; safer and more objective	-	[5,8,26,33-36]
Treatment			
EUS-guided sclerotherapy	Reducing injection dose, complications, and recurrence	Inferior to cyanoacrylate	[47-49]
EUS-guided tissue adhesive injection	Reducing injection dose, rebleeding rate and complications; faster and more firmly	Lack of recommended procedures and comparison among different needles	[36,41,42,51,54-59]
EUS-guided coil embolization	Improving technical success and reducing interventions and complications	Additional radiation exposure; expensive; technically demanding	[36,40,60-64]
EUS-guided coil embolization combined with tissue adhesive injection	Improving variceal occlusion, reducing rebleeding and reinterventions	Not clear about optimal coil numbers; technically challenging and time-consuming	[7,35,65-68]
Other EUS-guided injections	Novel alternatives; high clinical success rates with low risk for complications	Inferior variceal obliteration efficacy; lack of controlled studies	[40,69-72]
EUS-guided endovascular treatments	No radiation exposure; shorter puncture path; promising alternatives	Lack of controlled studies	[6,74-78]

EUS: Endoscopic ultrasound.

In conclusion, EUS technique advantages exist throughout the process, from diagnosis, preoperative assessment, treatment, and efficacy evaluation to follow-up in GV patients, and thus it is worthy of further research and promotion. EUS application by skilled EUS experts in proper GV patients at the right time will improve their diagnosis, efficacy, and whole GV management.

FOOTNOTES

Author contributions: Yang J and Zeng Y contributed equally to this work. Yang J, Zeng Y, and Zhang JW designed the study; Yang J and Zeng Y performed the literature search, analyzed the data, and wrote the manuscript; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Effectiveness of early colonoscopy in patients with colonic diverticular hemorrhage: A single-center retrospective cohort study

Chikamasa Ichita, Sayuri Shimizu, Akiko Sasaki, Chihiro Sumida, Takashi Nishino, Karen Kimura

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Abstract

BACKGROUND

Current guidelines recommend colonoscopy within 24 h for acute lower gastrointestinal bleeding; however, the evidence in support for colonic diverticular hemorrhage (CDH) indications remains insufficient.

AIM

To investigate the effectiveness of early colonoscopy on the length of hospital stay for CDH patients.

METHODS

We conducted a single-center retrospective cohort study. Patients who underwent colonoscopy within 24 h of presentation (early group) were compared with those who underwent colonoscopy beyond 24 h of presentation (elective group). The primary outcome was the length of hospital stay, and secondary outcomes were the identification of stigmata of recent hemorrhage (SRH), rebleeding, red blood cell transfusion more than 4 units, and interventional radiology and abdominal surgery after colonoscopy.

RESULTS

We identified 574 CDH cases. Patients were divided into the early (n = 328) and elective (n = 226) groups. After propensity score matching, 191 pairs were generated. The length of hospital stay did not significantly differ between the two groups (early group *vs* elective group; median, 7 *vs* 8 d; P = 0.10). The early group had a significantly high identification of SRH (risk difference, 11.6%; 95%CI: 2.7 to 20.3; P = 0.02). No significant differences were found in the rebleeding (risk difference, 4.7%; 95%CI: -4.1 to 13.5; P = 0.35), red blood cell transfusion more

than 4 units (risk difference, 1.6%; 95%CI: -7.5 to 10.6; P = 0.82), and interventional radiology and abdominal surgery rate after colonoscopy (risk difference, 0.5%; 95%CI: -2.2 to 3.2; P = 1.00).

CONCLUSION
Early colonoscopy within 24 h, on arrival for CDH, could not improve the length of hospital stay.

Key Words: Colonic diverticular hemorrhage; Colonic diverticular bleeding; Diverticular hemorrhage; Diverticular bleeding; Early colonoscopy; Colonoscopy

Core Tip: Current guidelines recommend colonoscopy within 24 h for acute lower gastrointestinal bleeding; however, the evidence in support for colonic diverticular hemorrhage (CDH) indications remains insufficient. We investigate the effectiveness of early colonoscopy on the length of hospital stay for CDH. The purpose of the study was to compare the length of hospital stay for CDH by dividing patients into two groups: An early group who underwent colonoscopy within 24 h and an elective group who underwent colonoscopy beyond 24 h and analysis was performed using propensity score matching. Early colonoscopy did not improve the length of hospital stay.

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INTRODUCTION

Among cases of acute lower gastrointestinal bleeding (ALGIB), colonic diverticular hemorrhage (CDH) is the most common, accounting for more than 60% of cases[1,2]. The clinical presentation of diverticular hemorrhage is usually hematochezia without fever or abdominal pain[3], and the diagnosis can be made with computed tomography (CT) findings, but colonoscopy is recommended for a definitive diagnosis [4,5].

Although various studies, including randomized controlled trials (RCTs)[6-9], have shown that current guidelines recommend colonoscopy within 24 h for ALGIB[2,4,5], no clear evidence has been established for CDH alone. The percentage of spontaneous hemostasis for CDH was as high as 60%-90% [2,10-12], while the prevalence of rebleeding was reported to be as high as 13%-48%[13]. Even if the source of bleeding is identified by early colonoscopy, it is unclear whether early colonoscopy reduces hospital stay.

Emergency colonoscopy is often difficult to perform because of colon preparation and personnel availability for the procedure. The purpose of this study was to determine whether early colonoscopy for diverticular hemorrhage improves hospital stay.

MATERIALS AND METHODS

Study design

This was a single-center, retrospective cohort study.

Patient selection

We included patients who presented to Shonan Kamakura General Hospital with hematochezia and underwent colonoscopy with a diagnosis of diverticular hemorrhage over a 5-year period from January 2017 to December 2021. Colonic diverticular hemorrhage was defined as 1) When the stigmata of recent hemorrhage (SRH) were found in the diverticulum[14] (Figures 1 and 2) When the colonoscopic findings ruled out diseases other than CDH.

Exposure

Patients were divided into early and elective groups. The early group was defined as patients who underwent colonoscopy within 24 h of arrival and the elective group was defined as patients who underwent colonoscopy beyond 24 h of arrival.

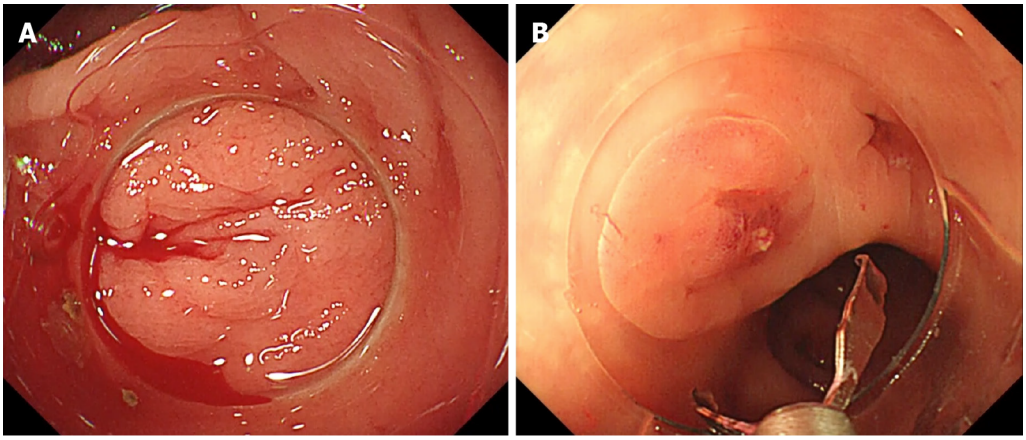

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Figure 1 Image of Stigmata of recent hemorrhage. A: Active bleeding; B: Non-bleeding visible vessel.

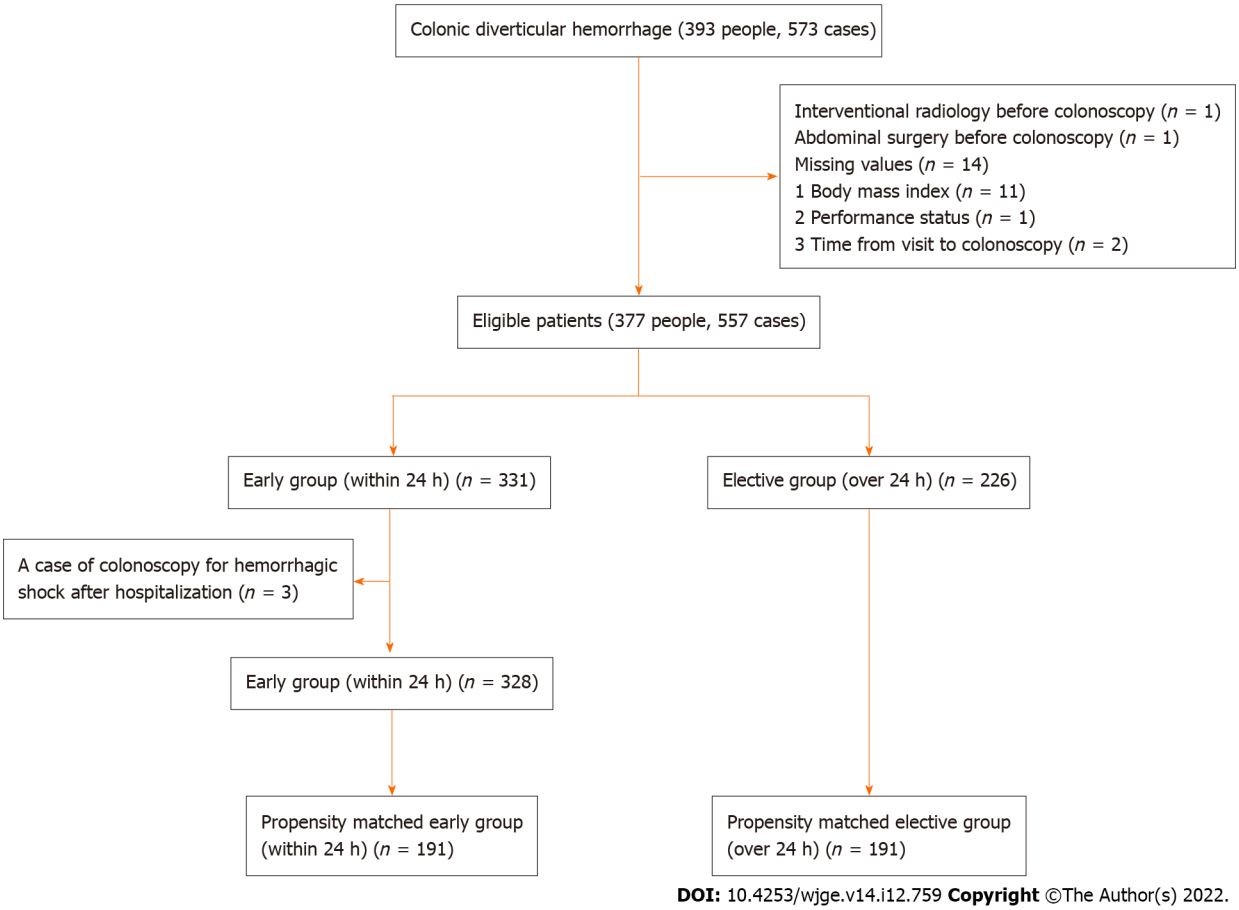

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Figure 2 Patient flow.

Exclusion criteria

Patients who underwent interventional radiology (IVR) or abdominal surgery prior to colonoscopy were excluded. Patients for which variables could not be obtained, such as time from visit to colonoscopy, were also excluded. Patients who presented without hemorrhagic shock but developed hemorrhagic shock during follow-up and were allocated to the early colonoscopy group were excluded because they were allocated to the early colonoscopy group due to deterioration of their condition, which may have disadvantaged the early group.

Variables and outcomes

Variables included age, sex, body mass index, smoking history, Eastern Cooperative Oncology Group

performance status (PS) over 3[15], comorbidities (hypertension, diabetes mellites, coronary artery disease, chronic kidney disease, hemodialysis), and the use of medications (antithrombotics and non-steroidal anti-inflammatory drugs, shock vitality at presentation, contrast CT findings, and blood sampling data (hemoglobin under 10 g/dL and platelet under 10000 /μL). Body mass index was categorized as underweight (< 18.5), normal weight (18.5-24.9), overweight (25-29.9), and obese (≥ 30). Smoking history was categorized as current, past, never, or no information. PS was determined by the condition of the patient at the time of the visit. Comorbidities were ascertained from the patient's medical history and medications at the time of presentation, and creatinine over 1.5 mg/dL was defined as chronic kidney disease. Antithrombotics use was defined as the prescription of aspirin, thienopyridine, warfarin, and direct oral anticoagulants. Shock vitality was defined as a shock index over 1 at presentation[16]. Contrast CT findings were classified as: (1) With an extravascular leak; (2) without an extravascular leak; or (3) without contrast CT, according to the contrast CT taken at the time of presentation. Extravascular leakage was defined as leakage of contrast medium into the colon at least in the delayed phase.

The primary outcome was the length of hospital stay. Secondary outcomes included the identification percentage of SRH[14], rebleeding, red blood cell transfusion more than 4 units, and the IVR and abdominal surgery after colonoscopy. IVR and abdominal surgery were defined as those performed to control diverticular bleeding or to control colonoscopy-related complications. The observation period for the outcome was during hospitalization.

Statistical analysis

We performed a propensity score matching analysis between the early and elective groups. This method can minimize the effect of selection bias and imbalances in patient backgrounds between the groups [17]. We estimated propensity scores with a logistic regression using early colonoscopy as a dependent variable and all covariates as independent variables. A one-to-one propensity score matching was performed utilizing the nearest neighbor method without replacement. The caliper width was set at 20% of the standard deviation of the propensity scores on the logit scale. Balances in baseline variables using standardized mean differences were also examined and values of < 0.1 were considered balanced[17].

In addition, two analyses were performed as sensitivity analyses. First, we performed an analysis in which the time to exposure was changed. The group with a time from visit to a colonoscopy of fewer than 12 h was defined as the early group (< 12 h), and the group with a time of 12 h or more was defined as the elective group (≥ 12 h). Propensity score matching was used for analysis in the same approach as in the main analysis. Second, we performed a multivariate analysis using the same covariates. We performed multivariable linear regression analyses for the length of hospital stay and performed multivariable logistic regression analyses for the identification of SRH, rebleeding, red blood cell transfusions more than 4 units, and IVR and abdominal surgery after colonoscopy.

Continuous variables are reported using medians and interquartile ranges, and categorical variables are reported using numbers and percentages. Continuous variables were compared using Mann-Whitney U tests and categorical variables were compared using chi-square tests. The risk difference with 95% confidence intervals (CI) was calculated for binary outcomes. We also calculated odds ratios (ORs) and their 95%CIs in the multivariable analysis. The two-sided significance level for all tests was $P < 0.05$. All analyses were performed using EZR version 1.55[18], a package for R statistical software (https://www.r-project.org/). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Ethics

All procedures were performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments. The study was reviewed and approved by the institutional review board of the Future Medical Research Center Ethical Committee (IRB No. TGE01304-024). Due to the observational study based on medical records without using samples taken from the human body, informed consent was obtained from all participants through the opt-out method on our hospital website.

RESULTS

During the study period, 573 CDH cases were identified. After applying the defined exclusion criteria, 557 cases were included in the present study. The patients were divided into the early (n = 328) and elective (n = 226) groups. One-to-one propensity score matching created 191 pairs of patients (Figure 2).

Baseline characteristics of eligible patients before and after propensity score matching are provided in Table 1. Before propensity score matching, sex, smoking history, shock vitals at presentation, and contrast CT findings were unbalanced, especially contrast CT findings were highly unbalanced. After propensity score matching, the baseline characteristics of both groups were nearly balanced.

Table 1 Patient background before and after propensity score matching

	Before propensity score matching			After propensity score matching		
	Early group (< 24 h)	Elective group (≥ 24 h)	SMD	Early group (< 24 h)	Elective group (≥ 24 h)	SMD
Variables	***n* = 328**	***n* = 226**		***n* = 191**	***n* = 191**	
Age, yr, median (IQR)	79.0 (71.0–84.0)	79.0 (72.3–84.0)	0.047	78.0 (70.0–84.0)	79.0 (71.5–84.0)	0.057
Male, *n* (%)	220 (67.1)	135 (59.7)	0.153	132 (69.1)	126 (66.0)	0.067
Body mass index, *n* (%)			0.087			0.094
< 18.5	46 (14.0)	18 (8.0)		15 (7.9)	18 (9.4)	
18.5-24.9	210 (64.0)	153 (67.7)		124 (64.9)	128 (67.0)	
25-29.9	76 (23.2)	76 (23.2)		45 (23.6)	39 (20.4)	
≥ 30	12 (3.7)	9 (4.0)		3 (1.6)	4 (2.1)	
Smoking			0.162			0.075
Current, *n* (%)	45 (13.7)	25 (11.1)		23 (12.0)	24 (12.6)	
Past, *n* (%)	104 (31.7)	64 (28.3)		64 (33.5)	58 (30.4)	
Never, *n* (%)	169 (51.5)	133 (58.8)		101 (52.9)	105 (55.0)	
No information, *n* (%)	10 (3.0)	4 (1.8)		3 (1.6)	4 (2.1)	
Performance status ≥ 3, *n* (%)	34 (10.4)	20 (8.8)	0.051	15 (7.9)	20 (10.5)	0.091
Comorbidities						
Hypertension, *n* (%)	210 (64.0)	152 (67.3)	0.051	124 (64.9)	122 (63.9)	0.022
Diabetes mellitus, *n* (%)	67 (20.4)	51 (22.6)	0.052	41 (21.5)	37 (19.4)	0.052
Coronary artery disease, *n* (%)	92 (28.0)	67 (29.6)	0.035	63 (33.0)	57 (29.8)	0.068
Chronic kidney disease, *n* (%)	33 (10.1)	28 (12.4)	0.074	22 (11.5)	25 (13.1)	0.048
Hemodialysis, *n* (%)	2 (0.6)	5 (2.2)	0.136	2 (1.0)	4 (2.1)	0.084
Medication						
Antithrombotics, *n* (%)	123 (37.5)	80 (35.4)	0.044	79 (41.4)	68 (35.6)	0.119
NSAIDs, *n* (%)	14 (4.3)	14 (6.2)	0.087	8 (4.2)	9 (4.7)	0.025
Shock vitality at presentation, *n* (%)	28 (8.5)	12 (5.3)	0.127	9 (4.7)	12 (6.3)	0.069
Contrast CT findings			0.811			0.027
With an extravascular leak, *n* (%)	129 (39.3)	17 (7.5)		17 (8.9)	17 (8.9)	
Without an extravascular leak, *n* (%)	159 (48.5)	170 (75.2)		138 (72.3)	140 (73.3)	
Without contrast CT, *n* (%)	40 (12.2)	39 (17.3)		36 (18.8)	34 (17.8)	
Blood sampling data						
Hemoglobin < 10 g/dL, *n* (%)	84 (25.6)	61 (27.0)	0.031	54 (28.3)	51 (26.7)	0.035
Platelet < 10000 /μL, *n* (%)	4 (1.2)	3 (1.3)	0.01	2 (1.0)	2 (1.0)	< 0.001

CT: Computed tomography; SMD: Standardized mean difference; IQR: interquartile range; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

Table 2 shows outcomes after propensity score matching. Length of hospital stay did not significantly differ between the two groups (early group *vs* elective group; median, 7 *vs* 8 d; $P = 0.10$). Among the secondary outcomes, the identification percentage of SRH was significantly higher in the early group (32.5% in the early group *vs* 20.9% in the elective group; risk difference, 11.6%; 95%CI: 2.7 to 20.3; $P = 0.02$). The rebleeding (28.8% *vs* 24.1%, respectively; risk difference, 4.7%; 95%CI: -4.1 to 13.5; $P = 0.35$), red blood cell transfusions more than 4 units (29.3% *vs* 27.7%, respectively; risk difference, 1.6%; 95%CI: -7.5 to 10.6; $P = 0.82$), and IVR and abdominal surgery after colonoscopy (2.1% *vs* 1.6%, respectively; risk difference, 0.5%; 95%CI: -2.2 to 3.2; $P = 1.00$) were not significantly different between the two groups.

Table 2 Outcomes of the main analysis

Outcomes	Early group (< 24 h)	Elective group (≥ 24 h)	Difference (95%CI)	*P* value
Primary outcome				
Length of hospital stay, days, median (IQR)	7 (7–9)	8 (7– 9.5)		0.10
Secondary outcomes				
Identification of stigmata of recent hemorrhage (%)	32.5 (62/191)	20.9 (40/191)	11.6 (2.7 to 20.3)	0.02
Rebleeding (%)	28.8 (55/191)	24.1 (46/191)	4.7 (-4.1 to 13.5)	0.35
Red blood cell transfusion ≥ 4 units (%)	29.3 (56/191)	27.7 (53/191)	1.6 (-7.5 to 10.6)	0.82
Interventional radiology and abdominal surgery (%)	2.1 (4/191)	1.6 (3/191)	0.5 (-2.2 to 3.2)	1.00

CI: Confidence interval; IQR: Interquartile range.

The results of the sensitivity analysis adopted 12 h as the exposure time, which was similar to those of the main analysis, however, the identification of SRH was different from that of the main analysis, and the superiority of early colonoscopy could not be demonstrated (Table 3). Sensitivity analyses with multivariate analysis showed similar results to the main analysis (Table 4).

DISCUSSION

The results of this study showed no significant difference in the length of hospital stay between early colonoscopy within 24 h and elective colonoscopy. Sensitivity analyses also showed similar results, indicating the robustness of the results. In contrast, the identification percentage of SRH, although a sensitivity analysis adopting an exposure time of 12 h did not show any advantage, was significantly higher in the early group. However, early colonoscopy did not indicate significant differences in rebleeding, red blood cell transfusion more than 4 units, and IVR and abdominal surgery after colonoscopy.

The randomized control trial (RCT) investigating the benefit of early colonoscopy, which currently has the most robust evidence, is a multicenter study published in 2020[9]. In this RCT, they found an increased identification percentage of SRH in the early group, but no significant difference in the rebleeding or length of hospital stay. Similar to our study, they were unable to demonstrate the benefit of early colonoscopy within 24 h. Although we did not recognize any RCTs that investigated the usefulness of early colonoscopy for CDH because definitive diagnosis is difficult to make before colonoscopy, we did recognize a large, receipt-based observational study in the United States (n = 20,100)[19]. In this United States study, early colonoscopy within 24 h also increased rebleeding and readmission. Some of the results indicated a disadvantage of early colonoscopy. There may be several reasons for this result. In case of the receipt database study: (1) It was difficult to obtain important information such as imaging information; (2) It did not ensure accurate diagnosis; and (3) It was difficult to obtain information on an hourly scale. In the present study: (1) Although various confounding factors can be compensated for with surrogate markers, confounding factors such as extravascular leakage findings on contrast CT could not be adequately addressed, which was important in this study; and (2) The accuracy of the diagnosis itself is likely to be unclear for diseases for which validation studies are insufficient. In such cases, the diagnosis may be incorrect if factors other than ICD-10 codes are not used appropriately. The Receipt Database Study can provide data on a daily scale, but it is difficult to provide data on an hourly scale. If the procedure was performed on the same day of admission, the range would be from 0 to 47 h, depending on the time at which the patient was admitted to the hospital. Few studies have evaluated the appropriate colonoscopy time for CDH. Although the present study was an observational study conducted at a single institution, the covariates were appropriately selected and adjusted, and robustness was demonstrated in the sensitivity analysis.

A possible reason for a prolonged length of hospital stay despite the identification of the source of bleeding in our study is the high rebleeding. Table 5 shows the hemostatic methods used in endoscopic hemostasis at the time of the main analysis of this study. In this study, the most common method of hemostasis in both the early and elective groups was the zipper clipping method. As shown in Table 6, the rebleeding of the zipper clipping method was considerably higher than that of other hemostatic techniques. In contrast, the direct clipping method and endoscopic band ligation (EBL) method have a significantly lower rebleeding (direct clipping method *vs* zippier clipping method *vs* EBL method; 9.3% *vs* 45.1% *vs* 10.3%). Especially for the EBL method, its low rebleeding and safety have been reported in recent years[20-24]. The general adoption of these hemostatic methods could improve rebleeding and shorten hospital stays. The number of EBL method cases in this study was inadequate because we

Table 3 Results of sensitivity analysis for a colonoscopy exposure time of 12 h

Outcomes	Early group (< 12 h)	Elective group (≥ 12 h)	Difference (95%CI)	*P* value
Primary outcome				
Length of hospital stay, median (IQR)	7 (6–9)	8 (7– 9)		0.09
Secondary outcomes				
Identification of stigmata of recent hemorrhage (%)	40.8 (51/125)	33.6 (42/125)	7.2 (-4.7 to 19.1)	0.30
Rebleeding (%)	37.6 (47/125)	25.6 (32/125)	12.0 (0.6 to 23.4)	0.06
Red blood cell transfusion ≥ 4 units (%)	30.4 (38/125)	28.8 (36/125)	1.6 (-9.7 to 12.9)	0.89
Interventional radiology and abdominal surgery (%)	2.4 (3/125)	3.2 (4/125)	-0.8 (-4.9 to 3.3)	0.74

CI: Confidence interval; IQR: Interquartile range.

Table 4 Results of sensitivity analysis using multivariate analysis

Primary outcome	Coefficient (95%CI)	*P* value
Length of hospital stay	0.08 (-0.71 to 0.87)	0.84
Secondary outcomes	Odds ratio (95%CI)	*P* value
Identification of stigmata of recent hemorrhage	1.76 (1.14–2.70)	0.01
Rebleeding	1.21 (0.78–1.86)	0.39
Red blood cell transfusion ≥ 4 units	0.91 (0.55–1.50)	0.71
Interventional radiology and abdominal surgery	0.93 (0.23–3.78)	0.92

CI: Confidence interval.

Table 5 Different hemostatic methods in the main analysis

Hemostatic method	Early group (< 24 h)	Elective group (≥ 24 h)	*P* value
Direct clipping method, *n* (%)	17/60 (28.3)	9/40 (22.5)	0.794
Zipper clipping, method, *n* (%)	30/60 (50.0)	21/40 (52.5)	
Endoscopic band ligation method, *n* (%)	13/60 (21.7)	10/40 (25.0)	

Table 6 Rebleeding rates by hemostatic methods, *n* (%)

Hemostatic method	Direct clipping method (*n* = 43)	Zipper clipping method (*n* = 82)	Endoscopic band ligation method (*n* = 47)
Rebleeding	4 (9.3)	37 (45.1)	5 (10.6)

adopted the EBL method in 2020. Further studies will be conducted in the future.

Limits of the study

There are several limitations associated with our study that should be noted. First, this is a single-center study, and generalizability to outside institutions is insufficient. Second, the localization of diverticula and the frequency of CDH are different among racial groups. It is unclear whether the Asian data can be applied to other races[25-28]. Third, the benefits of colonoscopy for CDH are not only potential in terms of reduced hospital stay associated with the colonoscopic hemostasis, but also an important factor in confirming the diagnosis. It should be noted that this study did not consider the benefits of the diagnostic factor.

Finally, this study focused on the time period from hospital visit to colonoscopy, not from the onset of hematochezia to colonoscopy. Therefore, the time period from the onset of hematochezia to colonoscopy may have differed from the actual time.

CONCLUSION

In conclusion, our study showed that early colonoscopy within 24 h did not improve the length of hospital stay for CDH. Early colonoscopy may not be necessary for all cases of CDH.

ARTICLE HIGHLIGHTS

Research background

Appropriate timing of colonoscopy for colonic diverticular hemorrhage is not well evidenced.

Research motivation

The motivation for this study is to investigate whether within 24 h is an appropriate timing for colonoscopy for colonic diverticular hemorrhage.

Research objectives

We aimed to compare the length of hospital stay for colonoscopy for colonic diverticular hemorrhage by dividing patients into two groups: early groups (within 24 h) and elective colonoscopy (after 24 h).

Research methods

A single-center retrospective study over 5 years compared the two groups using propensity score matching.

Research results

Early colonoscopy within 24 h did not significantly improve hospital stay.

Research conclusions

Early colonoscopy within 24 h for colonic diverticular hemorrhage may not improve length of hospital stay.

Research perspectives

Further research is needed to determine which patients really need early colonoscopy.

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FOOTNOTES

Author contributions: Ichita C, Shimizu S, Sasaki A, Sumida C, Nishino T, and Kimura K contributed equally to this work; Ichita C contributed to the planning, data gathering, literature review, writing and editing of this article; Shimizu S provided epidemiological advice and reviewed for statistical analysis; Sasaki A, Sumida C, Nishino T, and Kimura K provided professional suggestions in the conduct of the study; all authors commented on draft versions and approved the final version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the institutional review board of the Future Medical Research Center Ethical Committee (IRB No. TGE01304-024).

Informed consent statement: Due to the observational study based on medical records without using samples taken from the human body, informed consent was obtained from all participants through the opt-out method on our hospital website.

Conflict-of-interest statement: All the authors have no conflicts of interest directly relevant to the content of this article.

Data sharing statement: The original anonymous dataset is available on request from the corresponding author at ichikamasa@yahoo.co.jp.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was

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Observational Study

Our initial single port robotic cholecystectomy experience: A feasible and safe option for benign gallbladder diseases

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Abstract

BACKGROUND

Although single-port laparoscopic cholecystectomy has been performed for over 25 years, it is still not popular. The narrow working space used in this surgery limits the movement of instruments and causes ergonomic challenges. Robotic surgery not only resolves the ergonomic challenges of single-port laparoscopic surgery but is also considered a good option with its additional technical advantages, like a three-dimensional display and not being affected by tremors. However, the extent to which these technical and ergonomic advantages positively affect the surgical outcomes and how safe the single-port robotic surgeries need to be assessed for each particular surgery.

AIM

To evaluate the feasibility and safety of single-port robotic cholecystectomy for patients with cholelithiasis.

METHODS

The electronic records of the first 40 consecutive patients with gallbladder lithiasis who underwent single-port robotic cholecystectomy from 2013 to 2021 were analyzed retrospectively. In addition to the demographic characteristics of the patients, we analyzed American Society of Anesthesiologists (ASA) scores and body mass index. The presence of an accompanying umbilical hernia was also noted. The amount of blood loss during the operation, the necessity to place a drain in the subhepatic area, and the need to use grafts during the closure of the fascia of the port site were determined. Hospital stay, readmission rates, perioperative and postoperative complications, the Clavien-Dindo complication scores and postoperative analgesia requirements were also evaluated.

RESULTS

The mean age of the 40 patients included in the study was 49.5 ± 11.6 years, and 26 were female (65.0%). The umbilical hernia was present in 24 (60.0%) patients,

with a body mass index median of 29.3 kg/m^2 and a mean of 29.7 ± 5.2 kg/m^2. Fifteen (37.5%) of the patients were evaluated as ASA I, 18 (45.0%) as ASA II, and 7 (17.5%) as ASA III. The mean bleeding amount during the operation was 58.4 ± 55.8 mL, and drain placement was required in 12 patients (30.0%). After port removal, graft reinforcement during fascia closure was preferred in 14 patients (35.0%). The median operation time was 93.5 min and the mean was 101.2 ± 27.0 min. The mean hospital stay was 1.4 ± 0.6 d, and 1 patient was readmitted to the hospital due to pain (2.5%). Clavien-Dindo I complications were seen in 14 patients (35.0%), and five (12.5%) complications were wound site problems.

CONCLUSION

In addition to the technological and ergonomic advantages robotic surgery provides surgeons, our study strongly supports that single-port robotic cholecystectomy is a feasible and safe option for treating patients with gallstones.

Key Words: Cholecystectomy; Laparoscopic cholecystectomy; Robotic surgery; Single-port surgery; Single-port laparoscopic cholecystectomy; Single-port robotic cholecystectomy

Core Tip: We retrospectively analyzed 40 consecutive patients with cholelithiasis who underwent single-port robotic cholecystectomy from 2013 to 2021. We believe that the learning curve for single-port robotic cholecystectomy surgery is not long, and after a particular experience, the operation times are significantly shortened. Our data suggest that it is a safe surgery with acceptable intraoperative blood loss, no conversion, and no bile duct injury or postoperative bile leak. Our data also support more liberal graft use during the fascia closure. Single-port robotic cholecystectomy is a feasible and safe option that should be considered when treating patients with gallstones.

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INTRODUCTION

The first successful laparoscopic cholecystectomy (LC) was performed in 1985 and quickly became the preferred method for all benign gallbladder diseases. The laparoscopic approach was also favored for different surgeries and initiated the evolution of "single-port" and "robotic" surgeries. Single-port laparoscopic cholecystectomy (SPLC) was first introduced in 1995[1] and was shown to be a reasonable option for various surgeries like appendectomy[2] and colectomy[3].

The narrow working space in SPLC limits the movement of instruments and causes ergonomic challenges like crowding and collision between instruments. These technical difficulties have prevented SPLC from becoming the gold standard approach[4]. Robotic surgery gained popularity after 2010 and resolved the ergonomic challenges of single-port surgeries. Its additional technical advantages, like a three-dimensional display and not being affected by tremors, enable robotic surgery to be a good option for surgeries with single-port use. On the other hand, the extent to which these technical and ergonomic advantages positively affect surgical outcomes and how safe robotic surgeries are performed with a single port still need to be assessed.

To evaluate the feasibility and safety of single-port robotic cholecystectomy (SPRC) surgery, we analyzed the results of our first 40 consecutive SPRC operations for cholelithiasis from 2013 to 2021.

MATERIALS AND METHODS

The electronic patient records of the first 40 consecutive patients who underwent SPRC using the "da Vinci SI" platform (Intuitive Surgical, Sunnyvale, CA, United States) in our hospital between 2013 and 2021 were reviewed retrospectively. The indication for surgery in all patients was gallbladder lithiasis. No distinction was made between patients with or without symptoms, and patients with acute cholecystitis or suspected malignancy were not included in the group.

Gel port or SILS port was used in surgeries. The port was placed through an open technique, and a 3 cm incision was made from the umbilicus. After port placement, the patient was placed in a partial reverse Trendelenburg and right tilt position. The port was positioned with the camera trocar at the bottom and the working trocars at the top. After the camera trocar was inserted, the docking was done. Monopolar scissors and bipolar fenestrated forceps were placed in the study arms. A technique similar to LC was used in the surgeries. To reduce the risk of bile duct injuries and to avoid complications due to anatomical alterations, we used the "Critical View of Safety" technique introduced by Strasberg in all our SPRC surgeries[5]. Admittedly, the view achieved by SPRC is usually better than that of laparoscopy.

Similar care with laparoscopic surgeries in the postoperative period was applied. Patients were allowed to take fluids in the 2nd hour, mobilized at the 6th hour, and discharged within 1 d to 3 d post-surgery.

In addition to the demographic characteristics of the patients, we analyzed American Society of Anesthesiologists (ASA) scores and body mass indexes. The presence of an accompanying umbilical hernia was also noted. The amount of blood loss during the operation, the necessity to place a drain in the subhepatic area and the need to use grafts during the closure of the fascia of the port site were determined. Hospital stay, readmission rates, perioperative and postoperative complications, the Clavien-Dindo complication scores, and postoperative analgesia requirements were also evaluated.

Ertan Koç reviewed the calculations and statistical methods of this study.

RESULTS

The mean age of the 40 patients included in the study was 49.5 ± 11.6 years, and 26 patients were female (65.0%). The umbilical hernia was present in 24 (60.0%) patients with a body mass index median of 29.3 kg/m^2 and mean of 29.7 ± 5.2 kg/m^2. Fifteen (37.5%) of the patients were evaluated as ASA I, 18 (45.0%) as ASA II, and 7 (17.5%) as ASA III. The mean blood loss during the operation was 58.4 ± 55.8 mL, and drain placement was required in 12 patients (30.0%). After port removal, graft reinforcement for fascia closure was preferred in 14 patients (35.0%). We used a prolene graft for fascia closure reinforcement. After the fascial defect was primarily closed, a properly sized prolene graft was placed as an on-lay, and the graft was fixed with interrupted non-absorbable sutures.

The median operative time was 93.5 min and the mean time was 101.2 ± 27.0 min. The mean hospital stay was 1.4 ± 0.6 d, and 1 patient was readmitted to the hospital due to pain (2.5%). Clavien-Dindo I complications were seen in 14 patients (35.0%), and five complications (12.5%) were wound site problems (Table 1).

We also evaluated our 40 consecutive multi-port laparoscopic cholecystectomies performed in the last 6 mo to guide us in evaluating the results of our study. The average age of the patient in this group was 45.5. Fifteen of the patients were female and twenty-five were male. The mean BMI was 28.7 kg/m^2. For ASA scores, 14 patients were ASA 1, 23 were ASA 2, and 3 were ASA 3. One patient had an umbilical hernia. Thirteen patients were operated on for acute cholecystitis. Perioperative bleeding was minimal and drains were used in 4 patients; no grafts were used in any of the patients. The mean operative time was 54 min, and the average length of stay in the hospital was 1 d. A single dose of paracetamol was used as an analgesic postoperatively in 23 of the patients. Complications at the level of Clavien-Dindo 1 (2 of diarrhea, 1 of pain) developed in 3 patients postoperatively, but no patient required re-hospitalization (Table 2).

DISCUSSION

A systematic review published in 2021 evaluating the intraoperative and postoperative results of robotic cholecystectomy showed that the operating room time for robotic cholecystectomy is longer than its laparoscopic equivalent[6]. When the studies included in this review were evaluated, it was shown that the most critical factor that extended the operation time was the learning curve. While the time difference between the robotic and laparoscopic surgeries was more distinct in the studies before 2010, it was seen that there was less or no difference in the studies published in the following years. SPRC surgeries in our study lasted 60 to 207 min, with a median time of 93.5 min and an average of 101.2 ± 27 min. When we reviewed our data, we saw a similar trend in our study; the surgeries performed at the beginning of our learning curve took longer, and the operating times shortened over time. The increase in the operating room team's experience in preparing the robotic arrangement and the rapid replacement of hand tools shortened the surgery and operation times.

Perhaps the most significant limitation of our study was that the number of included surgeries was only 40. With this total number, it was impossible to perform subgroup analyses such as early and late periods, in which statistically significant differences could be revealed. On the other hand, our observation was similar to the results of a systematic review published in 2018 by Migliore *et al*[7] that showed the learning curve for SPRC surgery to not be long. After a particular experience, the operation

Table 1 Demographic and perioperative data of the patients

Characteristic	Parameter		
Age, yr	Min-Max: 26-73	Median: 48	mean ± SD: 49.5 ± 11.6
BMI, kg/m^2	Min-Max: 20.2–40.9	Median: 29.3	mean ± SD: 29.7 ± 5.2
Operation time, min	Min-Max: 60-207	Median: 93.5	mean ± SD: 101.2 ± 27.0
Amount of bleeding, mL	Min-Max: 15-250	Median: 50	mean ± SD: 58.4 ± 55.8
Length of hospital stay, d	Min-Max: 1-3	Median: 1	mean ± SD: 1.4 ± 0.6
Sex	Female	26	65
	Male	14	35
ASA score	I	15	37.5
	II	18	45
	III	7	17.5
Umbilical hernia	Present	24	60
	Absent	16	40
Drain	Present	12	30
	Absent	28	70
Graft	Present	14	35
	Absent	26	65
Postoperative complication	Present	14	35
	Absent	26	65
Readmission	Present	1	2.5
	Absent	39	97.5

Parameter data are presented as *n* and %, unless otherwise indicated. ASA: American Society of Anesthesiologists; BMI: Body mass index; SD: Standard deviation.

times were shortened significantly.

The same systematic review analyzed the conversion rates of SPRC surgeries. According to the results of the 13 studies included in the review, it was found that this rate was 4.2%, of which 2.2% were converted to multi-port laparoscopic surgery and 2% to open surgery[7]. We had no conversion among the 40 operations, probably due to our inclusion criteria. We did not prefer SPRC operations for patients with acute cholecystitis and its complications, such as perforation, or patients with malignant pathologies.

As a result of increasing experience and developing technological possibilities, the risk of complications in operations performed for benign gallbladder diseases has decreased significantly. Problems such as bile duct injuries and postoperative bile leaks decreased to 0.1%-0.3%. In our study, there were no patients with intraoperative bile duct injury or postoperative bile leakage. These data were again attributed to our patient selection criteria and our limited number of surgeries. We anticipate that this technique will also become one of our options in non-elective gallbladder surgeries and malignant diseases soon. We plan to evaluate whether SPRC surgeries performed for these more complicated aetiologies will affect our complication rates.

The mean perioperative blood loss in our SPRC surgeries was 58 mL. This loss was similar to the blood loss in other cholecystectomy operations where we use different techniques like LC or SPLC and is also comparable with literature data. Our "learning curve" discussion about the operation time may also be valid for our generous drain preference in this cohort (12 surgeries – 30.0%), and we hypothesize that we will have a decreasing trend in the coming years.

An umbilical hernia was present in 24 patients (60.0%). This rate is higher than expected, likely due to the addition of patients with fascia defects detected by ultrasonography to patients with clinically significant hernia. At the end of the surgery, graft reinforcement was preferred in 14 patients (35.0%) during the closure of the port site. In the follow-up, an incisional hernia was observed in 1 patient (2.5%) in whom we did not use a graft. A meta-analysis by Jensen *et al*[8] showed that the risk of incisional hernia development in patients who underwent robotic cholecystectomy ranged from 0% to 16.7%. We also know that prophylactic graft use in the laparoscopic method reduces the risk of incisional hernia

Table 2 Demographic and perioperative data of our last 40 consecutive laparoscopic cholecystectomy patients

Feature		Value
Average age, yr		45.5
BMI, kg/m^2		28.7
Operation time, min		54
Amount of bleeding, mL		10
Length of hospital stay, d		1
Sex	Female	15
	Male	25
ASA score	I	14
	II	23
	III	3
Umbilical hernia	Absent	39
	Present	1
Drain	Absent	36
	Present	4
Graft	Absent	40
	Present	0
Postoperative complication	Absent	37
	Present	3
Readmission	Absent	40
	Present	0

ASA: American Society of Anesthesiologists; BMI: Body mass index.

development[9]. Our study had only 1 patient with an incisional hernia, and we did not use a graft for that patient. All those facts support more liberal graft use during the fascia closure. Graft reinforcement should be considered more frequently, especially in patients with a body mass index > 30 kg/m^2, over 65 years of age, who are diabetic, and who have a chronic obstructive pulmonary disease with impaired wound healing and a high risk of incisional hernia.

It is known that wound site problems are more significant in laparoscopic and robotic cholecystectomy operations performed *via* a single port when compared with multiple ports[10,11]. While the general wound site problems reported for SPRC surgeries accounted for 5%, it was found that this problem was seen in 5 patients (12.5%) in our study. The difference between the literature and the results of our study may be due to the definition of 'wound problem'. While in most series only patients with surgical site infection and significant seroma were included in this group, we added patients with surgical site dehiscence and incision healing problems to the list.

LC operations performed using a single port have better cosmetic results than LC operations performed using multiple ports and provide higher patient satisfaction[10,11]. However, in robotic surgery, there is no study evaluating the impact of the port number on cosmetic results and patient satisfaction. The general belief is that patients are happier with a single incision, and our observations support this data.

There is no robust data that support that any of the surgical options for cholecystectomy have an impact on postoperative pain. A systematic review published in 2021 analyzed 15 studies for postoperative pain. It was concluded that it is impossible to say whether there is a difference between patients who underwent robotic surgery or LC due to different study methodologies and pain assessment methods[6]. In a recently published study, it was found that the pain scores of patients who underwent SPRC were lower than the scores of patients who underwent LC *via* a single port[12]. It was observed that the pain scores of the patients included in our study were low, and pain control could be achieved effectively using single (paracetamol) or dual (paracetamol and nonsteroidal anti-inflammatory) painkillers. In 1 patient included in the study, post-discharge pain scores remained high, and he was re-hospitalized to maintain pain control.

Sun *et al*[13] published a systematic review and meta-analysis in 2018, which compared SPRC and multi-port laparoscopic cholecystectomy surgeries. They concluded that the risk of incisional hernia and the high cost of the procedure should be considered when performing SPRC. However, their main conclusion was that, so far, the advantages and disadvantages of SPRC still have not been studied extensively and we need more high-quality studies and data to be able to comment on robot-assisted cholecystectomy operations. Indeed, there is also a lack of concrete evidence from comparisons of the advantages and disadvantages of the single-port *vs* multi-port robotic cholecystectomy operations, with the exceptions of features related to ergonomics and technical components. More high-quality studies are also needed for applicability in more complex gallbladder diseases.

Another limitation of our study was the inability to evaluate whether SPRC increased the cost of treating benign gallbladder diseases. The cost of the operations showed a significant difference during the study period (2013-2021) due to a number of reasons. According to current calculations, the mean cost for SPRC is $6659 and for multi-port laparoscopic cholecystectomy is $2439.

CONCLUSION

The findings from this study, which we performed on 40 consecutive patients, strongly support the view that SPRC is a feasible and safe surgery. Considering the technological and ergonomic advantages it provides to the surgeon, SPRC seems to be an excellent option that should be considered for all benign gallbladder pathologies. It would be appropriate to confirm this inference with randomized controlled studies with a large number of patients in the near future.

ARTICLE HIGHLIGHTS

Research background

Single-port laparoscopic cholecystectomy has been performed for over 25 years but is not popular. The narrow working space in this surgery limits the movement of instruments and causes ergonomic challenges. Robotic surgery resolves the ergonomic challenges. However, the extent to which these technical and ergonomic advantages positively affect the surgical outcomes and the safety of the single-port robotic surgeries need to be assessed.

Research motivation

Our first motivation for the study was to determine the feasibility and safety of single-port laparoscopic cholecystectomy. We also evaluated patient outcomes after robotic surgery.

Research objectives

Our main objective was to evaluate the safety of single-port laparoscopic cholecystectomy by determining intraoperative blood loss, conversion rate, and risk of bile duct injury or postoperative bile leak. We also determined the necessity of grafts during fascia closure.

Research methods

Our research methodology was retrospective electronic patient record evaluation.

Research results

We observed that the mean blood loss during the operation was 58.4 mL, and drain placement was required in 12 patients (30.0%). The median operative time was 93.5 min. We hypothesize that experience of the surgeon will have a positive effect on those numbers, and future studies will have better results. After port removal, graft reinforcement for fascia closure was preferred in 14 patients (35.0%). One patient was readmitted to the hospital due to pain (2.5%). Clavien-Dindo I complications were seen in 14 patients (35.0%), and 5 complications (12.5%) were wound site problems. These data support the safety of single-port robotic cholecystectomy.

Research conclusions

The findings of this study, which we performed on 40 consecutive patients, strongly supported the view that single-port robotic cholecystectomy is a feasible and safe surgery. Considering the technological and ergonomic advantages it provides to the surgeon, single-port robotic cholecystectomy seems an excellent option that should be considered for all benign gallbladder pathologies.

Research perspectives

It would be appropriate to confirm our results with randomized controlled studies to be conducted with more patients in the near future. Also, comparing single-port laparoscopic cholecystectomy and single-

port robotic cholecystectomy will be helpful.

FOOTNOTES

Author contributions: Rasa HK contributed to conceptualization of the study, methodology, writing, review and editing of the manuscript, and project administration; Erdemir A contributed to conceptualization of the study, methodology, formal analysis of the data, investigation into the literature and writing of the original draft of the manuscript; both authors read and approved the final manuscript.

Institutional review board statement: The study was conducted following the Declaration of Helsinki (as revised in 2013) and was approved by Anadolu Medical Center Hospital review board and ethics committee (ASM-EK-22/186).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Data sharing statement: The datasets analyzed during the current study are available in the hospital's "electronic patient records" and from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

Randomized Clinical Trial

High-flow oxygen *via* oxygenating mouthguard in short upper gastrointestinal endoscopy: A randomised controlled trial

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Abstract

BACKGROUND

Anaesthetic care during upper gastrointestinal (GI) endoscopy has the unique challenge of maintaining ventilation and oxygenation *via* a shared upper airway. Supplemental oxygen is recommended by international society guidelines, however, the optimal route or rate of oxygen delivery is not known. Various oxygen delivery devices have been investigated to improve oxygenation during upper GI endoscopy, however, these are limited by commercial availability, costs and in some cases, the expertise required for insertion. Anecdotally at our centre, higher flows of supplemental oxygen can safely be delivered *via* an oxygenating mouthguard routinely used during upper GI endoscopic procedures.

AIM

To assess the incidence of hypoxaemia (SpO_2 < 90%) in patients undergoing upper GI endoscopy receiving supplemental oxygen using an oxygenating mouthguard at 20 L/min flow compared to standard nasal cannula (SNC) at 2 L/min flow.

METHODS

A single centre, prospective, randomised clinical trial at two sites of an Australian

tertiary hospital between October 2020 and September 2021 was conducted. Patients undergoing elective upper gastrointestinal endoscopy under deep sedation were randomised to receive supplemental oxygen *via* high-flow *via* oxygenating mouthguard (HFMG) at 20 L/min flow or SNC at 2 L/min flow. The primary outcome was the incidence of hypoxaemia of any duration measured by pulse oximetry. Intraprocedural-related, procedural-related, and sedation-related adverse events and patient-reported outcomes were also recorded.

RESULTS

Three hundred patients were randomised. Eight patients were excluded after randomisation. 292 patients were included in the intention-to-treat analysis. The incidence of hypoxaemia was significantly reduced in those allocated HFMG. Six patients (4.4%) allocated to HFMG experienced an episode of hypoxaemia, compared to thirty-four (22.1%) patients allocated to SNC (P value < 0.001). No significant difference was observed in the rates of adverse events or patient-reported outcome measures.

CONCLUSION

The use of HFMG offers a novel approach to reducing the incidence of hypoxaemia during short upper gastrointestinal endoscopic procedures in low-risk patients undergoing deep sedation.

Key Words: Upper gastrointestinal endoscopy; Supplementary oxygen; Hypoxaemia; Oxygenating mouthguard

Core Tip: This randomised controlled trial compared the incidence of hypoxaemia in those receiving supplemental oxygen at 20 L/min *via* an oxygenating mouthguard to those receiving supplemental oxygen at 2 L/min *via* standard nasal cannula during upper gastrointestinal endoscopy performed under deep sedation. A statistically significant difference in the incidence of hypoxaemia was demonstrated. No significant difference was observed in rates of adverse events or patient-reported outcome measures. We conclude that the use of supplemental oxygen at 20 L/min *via* an oxygenating mouthguard offers a novel approach to reducing the incidence of hypoxaemia in patients undergoing upper gastrointestinal endoscopy under deep sedation.

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INTRODUCTION

Upper gastrointestinal (GI) endoscopic procedures are commonly performed under monitored anesthesia to facilitate endoscopic examination. Anaesthetic care during upper GI endoscopy has the unique challenges of balancing adequate patient sedation while maintaining sufficient ventilation and oxygenation *via* a shared upper airway[1]. In addition, anaesthetic agents routinely used during sedation for GI endoscopies, such as propofol, in combination with benzodiazepines and opioids can cause respiratory depression, predisposing patients to upper airway obstruction, hypoventilation, and hypoxaemia[2]. Therefore, supplementary oxygen during upper GI endoscopy under deep sedation is considered the standard practice to reduce the incidence and severity of hypoxaemia[3].

Although supplemental oxygen is a recommendation of various national and international societies, it is unclear what the optimal routes or rates of supplemental oxygen delivery are[4,5]. The incidence of hypoxaemia during upper GI endoscopy with deep sedation is common, and reported to occur in up to 33% of procedures depending on the route and rate of supplemental oxygen used[6,7]. Although transient and mild episodes of hypoxaemia are likely inconsequential, prolonged or severe hypoxaemia is associated with tachycardia and myocardial ischemia[8,9]. Various oxygen delivery devices have been investigated to improve oxygenation during upper GI endoscopy. These include standard nasal cannula (SNC), high-flow nasal cannula (HFNC), modified bite blocks, modified face masks and other more invasive nasopharyngeal (such as Wei Nasal Jet tube) and oropharyngeal devices (such as a gastro-laryngeal tube)[10-12]. The principles underlying these airway devices include the delivery of higher

fractionated oxygen (FiO_2) with or without positive pressure ventilation[1].

Oxygen supplementation *via* SNC is the most common approach to oxygen delivery during upper gastrointestinal endoscopy[11]. However, its use is limited to flow rates of 6 L/min, as higher flow rates cause drying of the nasal passages and nasal mucosa irritation. The advent of HFNC has circumvented these limitations of SNC by passing supplementary oxygen through a humidifier. Flows of up 60 L/min can be achieved, which has added advantages of generating a positive end-expiratory pressure, and reducing physiological dead space, whilst delivering higher FiO_2[7]. The routine use of HFNP is limited by its high costs and the required training and education to set up. Other airway devices described above are limited by the commercial availability, costs and expertise required for insertion[11].

At our centre, an oxygenating mouthguard (Oxyguard™; North Yorkshire, England) is routinely used for all upper GI endoscopy procedures to minimise dental injury and damage to the endoscope, whilst maintaining the mouth in an open position during the procedure. This mouthguard can be used to deliver supplementary oxygen by directing the flow of oxygen *via* a dedicated oxygen port into the oral and nasal cavities simultaneously (Figure 1A-D). It is held in place with a rubber strap wrapped around a patient's head (Figure 1E). This product is commercially available throughout Australia, Europe, and South Africa at the time of writing. Though the benefit of using 3L/min supplementary oxygen *via* this mouthguard in alleviating hypoxaemia during gastroscopy has been demonstrated, compared to a standard plastic mouthguard using room air, there are no publications to date on the use of high flows of supplemental oxygen[13]. Anecdotally, our team found that higher flows of supplemental oxygen can be safely delivered *via* this mouthguard during upper GI endoscopic procedures. An impetus to further investigate the clinical efficacy of delivering higher flows of oxygen *via* this mouthguard was the recent publication by Lin *et al*[7] The use of HFNC at 60 L/min, when compared to a supplemental oxygen flow rate of 2 L/min in a low-risk population for sedation-related adverse events undergoing a short gastroscopy performed under propofol sedation, demonstrated a significant reduction in the incidence of hypoxia (defined as oxygen saturation (SpO_2) < 90% and ≥ 75% for < 60 s) and severe hypoxia (defined as SpO_2 < 75% for any duration, or SpO_2 < 90% and ≥ 75% for ≥ 60 s) from 8.4% to 0% (P value < 0.001) and from 0.6% to 0% (P value = 0.03), respectively[7].

In this article, we report a randomised controlled trial on the novel use of high-flow supplemental oxygen *via* an oxygenating mouthguard in low-risk patients of sedation-related adverse events under propofol sedation.

MATERIALS AND METHODS

This is a single-centre, prospective, randomised clinical trial conducted at two sites of an Australian tertiary health service, between October 2020 and September 2021. Local ethics committee approval (ND 63130/2020) and registration at ANZCTR.org.au (ACTRN12620000930987) were attained before patient recruitment.

All patients referred for an endoscopy at our centre were considered during the study period. Inpatients scheduled a non-emergent upper GI endoscopy (gastroscopy, endoscopic retrograde cholangiopancreatography (ERCP), upper enteroscopy or upper endoscopic ultrasound (EUS), alone or in combination with another upper GI endoscopy) were offered the patient information and consent form (PICF) at least 12 h before their scheduled procedure. Non-emergent endoscopy was defined as a patient with vital signs within normal limits without evidence of upper GI bleeding or an active infection. Outpatients scheduled for upper GI endoscopies were sent the PICF *via* post or email. Patients scheduled for a combined lower GI tract endoscopy (such as colonoscopy, lower enteroscopy or lower endoscopic ultrasound) or scheduled for endoscopist administered sedation lists were excluded.

Patients scheduled for upper GI endoscopy were assessed for the following inclusion and exclusion criteria by an investigator at the time of their procedure. Inclusion criteria: (1) Age >18 years; (2) Ability to provide informed consent; and (3) An anticipated endoscopic procedure time of fewer than 20 min, as assessed by the accredited gastroenterologist or surgeon responsible for the case. Exclusion criteria: (1) America Society of Anesthesiologist[14] class greater than III; (2) Mallampati score[15] of greater than 3; (3) Body mass index > 35 kg/m^2; (4) Supplementary oxygen dependence; (5) Pregnancy; (6) Deemed high-risk of a sedated-related adverse event by the duty anaesthetist; and (7) Anticipated requirement or plan for general anaesthesia involving airway instrumentation including a laryngeal mask or tracheal intubation.

Intervention

Enrolled participants were randomly assigned to one of two groups: high-flow *via* oxygenating mouthguard (HFMG) at 20 L/min or SNC (Softi Smoothflow®; Victoria, Australia) at 2 L/min flow. Of note, the design of this SNC allows oxygen delivery through one nasal prong and sampling of expired carbon dioxide from the other prong simultaneously.

Supplemental oxygen at 20 L/min was supplied from a high-flow oxygen rotameter and delivered *via* a dedicated oxygen port as depicted in Figure 1A-E. Patients allocated to the SNC received oxygen at a fixed rate of 2 L/min. Initial flow rates were maintained throughout the endoscopic examination unless

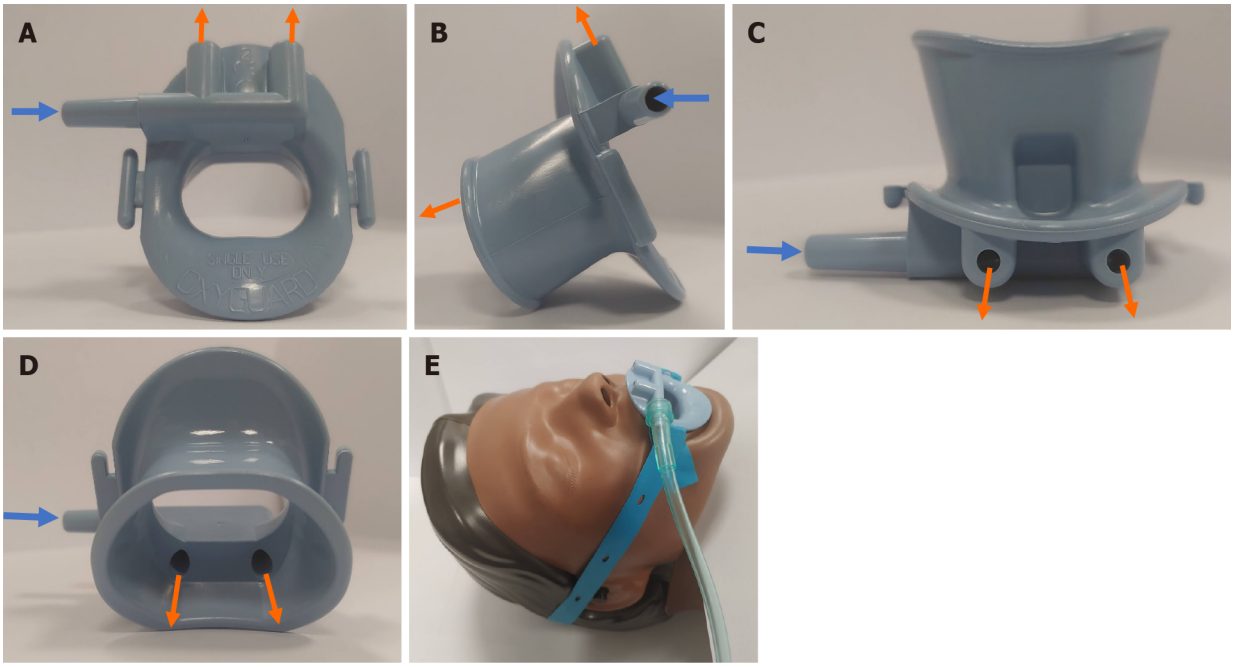

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Figure 1 Standard Oxyguard™ and its set-up. A: Front profile; B: Right-sided profile, C: Top profile; D: Rear profile; E: Standard Oxyguard™ with rubber strap demonstrating its set up. The blue arrow describes the direction of oxygen flow into the mouthguard. The orange arrow describes the direction of oxygen flow out of the mouthguard.

a hypoxemic event occurred. At the discretion of the anesthetist, the rate or route of oxygen delivery could be changed.

The endoscopic procedure and anaesthetic care

Proceduralists and anaesthesiologists were instructed to provide usual care except for the assigned initial oxygen delivery method and rate. Standard monitoring, including heart rate, blood pressure and SpO_2 were measured and recorded. The use of capnography was at the discretion of the duty anaesthetist. All physiological measurements were recorded using the GE Datex-Ohmeda Aisys Anaesthesia Machine (General Electric, Boston, United States).

Gastroscopy, EUS and enteroscopy were performed in the left lateral position, unless performed together with an ERCP which were performed in the semi-prone position under intravenous sedation with propofol with or without benzodiazepine and/or opioids.

Data on participants' symptoms post-procedure were collected using a Likert scale questionnaire (Supplementary Appendix III) before the patient's discharge from the endoscopy unit. Incomplete patient-reported symptom forms were excluded.

Outcome measures

The primary outcome was the occurrence of hypoxaemia, defined as $SpO_2 < 90\%$, of any duration measured by pulse oximetry during the procedure[7,16,17].

Secondary outcomes included the lowest SpO_2 measured by pulse oximetry during the procedure, the incidence of hypoxaemia defined as mild (SpO_2 90%-94%), moderate (SpO_2 89%-76%) and severe ($SpO_2 \leq$ 75%) of durations less than 1 minute, between 1 and 5 minutes and more than 5 min, procedure-related adverse events, sedation-related events, and patient-reported symptoms.

A clinically significant episode of hypoxaemia was defined as a need to change the flow or method of oxygen delivery that the patient was randomised to in response to an episode of hypoxaemia.

In addition, a posthoc analysis of the incidence of hypoxaemia defined as $SpO_2 < 85\%$ was performed [18].

Intraprocedural-related adverse events included a need to pause or stop the procedure due to an episode of oxygen desaturation or as directed by the duty anaesthetist. Procedure-related complications including bleeding requiring intervention, perforation, and post-procedure complications including pain, bleeding or sepsis necessitating a hospital admission or delayed discharge from the endoscopy unit were also recorded. Sedation-related adverse events included hypotension, bradycardia, tachycardia, seizure, cardiac arrest, nausea or vomiting, recovery agitation and delayed recovery whilst in the procedure room were noted.

Patient-reported symptoms after the procedure included overall comfort, abdominal pain, abdominal bloating, nose, mouth or throat dryness or pain, and headache.

Endoscopy procedure time was routinely collected and defined as the time the endoscope entered and exited the oral orifice. When more than one upper GI endoscopy was performed, the endoscopy procedure time was defined as the time of the first endoscope entering the oral orifice and the last endoscope exiting. Anaesthetic time was defined as the duration of time during which intravenous propofol was administered.

Randomisation

Allocation was pre-defined through an online research randomiser (https://www.randomizer.org). The allocation was placed into 300 sealed opaque envelopes by an independent person who was not a member of the research team. The envelopes were labelled from 1 to 300 and were consecutively opened. The envelopes were evenly split between the two sites and continued to be evenly distributed until the last patient was recruited.

Blinding

The clinical care team (*e.g.*, anaesthetists, endoscopists, nurses) was advised of the patient's randomisation. Patients were not blinded to their allocation due to the obvious difference in the oxygen delivery devices.

Sample size calculation

Two-tailed 0.05 alpha error and power of 80% were used for the sample size calculation. A 10% loss after randomisation was also accounted for. We aimed to enrol 300 patients, based on an anticipated difference of 8.4% previously observed when comparing HFNC at 40-60 L/min and 2 L/min in upper GI endoscopy[7]. The incidence rates used were 9.4% and 1.0% in the control and interventional group, respectively.

Statistical analyses

SPSS was used for statistical analyses. Collected data were summarised as mean ± standard deviation (SD) or median (25^{th} and 75^{th} percentile) for continuous data, and as frequency and percentages for categorical data. For continuous data, the characteristics, and outcomes for the two groups were compared using Student's *t*-test or Wilcoxon-Mann-Whitney test based on the normality assumption. Categorical data were compared with Chi-square or Fisher's exact test as appropriate. A P value of < 0.05 was considered significant. Statistical analyses were performed with SPSS Version 28.0.1.1.

RESULTS

From October 2020 to September 2021, 300 patients were enrolled and randomised; 8 patients were excluded after randomisation. Five patients were excluded as the accredited anaesthesiologist deemed the patient not appropriate for the study (*e.g.*, change in the anaesthetic plan after review by the accredited anaesthetist for intubation under general anaesthesia), one patient's procedure was cancelled by the proceduralist as anti-coagulation was not ceased as planned, one patient's procedure was abandoned due to the presence of food in the oesophagus and another patient was unable to wear the oxygenating mouthguard as their mouth opening was insufficient.

A total of 292 patients were included in our intention-to-treat analysis. Figure 2 flow chart describes the patient allocation.

In addition, ten patients did not receive their allocated rate and/or route of supplementary oxygen. Three of these patients allocated to HFMG did not receive 20 L/min as per protocol. Instead, two patients received 10 L/min, and one patient received 15 L/min *via* the mouthguard. Furthermore, seven patients were incorrectly allocated to the wrong group. Four patients allocated to HFMG received 2 L/min *via* SNC, and three patients allocated to SNC received 20 L/min *via* mouthguard. A per-protocol analysis was performed to determine the impact of these discrepancies on the primary outcome. The three patients receiving 10 L/min and 15 L/min *via* mouthguard were excluded from the per-protocol analysis. The per-protocol analysis for the primary outcome is described below in the results.

The baseline characteristics of the two groups are described in Table 1.

Details of the anaesthetic care and endoscopy procedure are summarised in Tables 2 and 3, respectively. Of note, the weighted dose of propofol per hour of the two groups and the number of anaesthetic agents used were similar. In addition, the duration of sedation and upper GI endoscopies performed were comparable between the two groups. Most procedures (86.3%) were 20 minutes or shorter. A sub-group analysis of longer procedures for the primary outcome was performed and is described below. More than half (52.7%) of the upper GI endoscopies were diagnostic. The most common procedures were gastroscopies (69.2%) and ERCPs (22.6%).

Table 1 Characteristics of the patient at baseline (*n*, %)

Characteristics	SNC (*n* = 154)	HFMG (*n* = 138)
Age (median, IQR)	64, 56 to 72	59, 48.5 to 69.5
Male	71, 46.1%	67, 48.6%
Weight, kg (mean, SD)	76.4, 13.6	76.1, 14.8
BMI, kg/m^2 (mean, SD)	26.6, 4.1	26.4, 3.9
ASA classification, I/II/III	14/67/73, 9.1%/43.5%/47.4%	16/58/64, 11.6%/42.0%/46.4%
Mallampati class, I/II/III	54/70/30, 35.1%/45.4%/19.5%	48/70/20, 34.8%/50.7%/14.5%
Baseline oximetry, SpO_2 (median, IQR)	97%, 95% to 99%	98%, 97% to 99%
Past medical history		
Current smoking history	14, 9.1%	14, 10.1%
Obstructive sleep apnoea	8, 5.2%	6, 4.3%
Hypertension	69, 44.8%	46, 33.3%
Ischemic heart disease	19, 12.3%	9, 6.5%
Diabetes mellitus	34, 22.1%	33, 23.9%
Dyslipidemia	36, 23.4%	26, 18.8%
Chronic obstructive pulmonary disease	8, 5.2%	11, 8%
Asthma	9, 5.8%	11, 8%
Cirrhosis	25, 16.2%	34, 24.6%
Orthotopic liver transplantation	19, 12.3%	25, 18.1%

ASA: American Society of Anesthesiologists; BMI: Body mass index; HFMG: High-flow *via* oxygenating mouthguard; IQR: Interquartile range; SpO_2: Oxygen saturation; SD: Standard deviation; SNC: Standard nasal cannula.

Table 2 Anaesthetic care parameters (*n*, %)

Anaesthetic care	SNC (*n* = 154)	HFMG (*n* = 138)	*P* value
Duration of sedation, min (median, IQR)	12, 6.9 to 17.1	12, 6.5 to 17.5	0.421
Propofol dose, mg/kg/hr (median, IQR)	13.3, 8.5 to 18.1	14.1, 7.8 to 20.5	0.189
Opioids	89, 57.8%	73, 52.9%	0.631
Fentanyl	52, 33.8%	40, 29.0%	
Alfentanil	37, 24.0%	33, 23.9%	
Midazolam	26, 16.9%	23, 16.7%	0.961

HFMG: High-flow *via* oxygenating mouthguard; IQR: Interquartile range; SNC: Standard nasal cannula.

Outcomes and estimate

We found a statistically significant difference in the primary outcome of hypoxaemia (SpO_2 < 90%) of any duration. Six patients (4.4%) allocated to HFMG experienced at least an episode of hypoxaemia compared to 34 (22.1%) patients allocated to SNC (Table 4). In addition, a statistically significant difference in all secondary outcomes was also observed between the two groups. No episode of severe hypoxaemia (SpO_2 ≤ 75%) was observed in the HFMG group (Figure 3).

A per-protocol analysis performed for the primary outcome of hypoxaemia still demonstrated a statistically significant difference (*P* value < 0.001). A subgroup analysis of longer procedures for the primary outcome was performed. However, the number of patients and event rates were too few to provide a meaningful interpretation. Two patients (8.7%) allocated to HFMG, and four patients (23.5%) allocated to SNC experienced an episode of hypoxaemia in procedures longer than 20 min. The majority (68.3%) of procedures longer than 20 minutes were therapeutic, with ERCPs (48.8%) the most common procedure.

Table 3 Upper gastrointestinal endoscopy parameters (*n*, %)

Endoscopy parameters	SNC, (*n* = 154)	HFMG, (*n* = 138)	*P* value
Duration of procedure, min (median, IQR)	10, 5.5 to 14.5	10, 4.5 to 15.5	0.684
Types of procedure			0.175
Diagnostic Procedure	87, 56.5%	67, 48.6%	
Therapeutic Procedure	67, 43.5%	71, 51.4%	
Types of upper GI endoscopy			0.27
Gastroscopy	106, 68.8%	96, 69.6%	
Duodenoscope	1, 0.6%	1, 0.7%	
ERCP	32, 20.8%	34, 24.6%	
EUS	12, 7.8%	3, 2.2%	
Gastroscopy + EUS	3, 1.9%	4, 2.9%	

EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholangiopancreatography; HFMG: High-flow *via* oxygenating mouthguard; SNC: Standard nasal cannula.

Table 4 Primary and secondary end points for the intention-to-treat analysis end point (*n*, %)

End point	SNC (*n* = 154)	HFMG (*n* = 138)	*P* value
Primary endpoint			
SpO_2 < 90% of any duration	34, 22.1%	6, 4.4%	< 0.001
Secondary endpoint			
Lowest SpO_2 (median, IQR)	95%, 91% to 99%	98%, 96.5% to 99.5%	< 0.001
Any episode of hypoxaemia	74, 48.1%	26, 18.8%	< 0.001
SpO_2 90%-94% of any duration	40, 26.0%	20, 14.5%	0.015
SpO_2 76%-89% of any duration	28, 18.2%	6, 4.3%	< 0.001
SpO_2 ≤ 75% of any duration	6, 3.9%	0, 0%	0.019
Clinically significant episode of hypoxaemia[1]	32, 20.8%	1, 0.7%	< 0.001
SpO_2 < 85% of any duration	19, 12.3%	3, 2.2%	0.001

[1]Clinically significant episode of hypoxemia is defined as a need to change in flow or method of oxygen delivery that the patient was originally randomised to.

HFMG: High-flow *via* oxygenating mouthguard; IQR: Interquartile range; SpO_2: Oxygen saturation; SNC: Standard nasal cannula.

A clinically significant episode of hypoxaemia requiring a need to change the flow or route of oxygen delivery was observed in one patient (0.7%) in the HFMG and 32 patients (20.8%) in the SNC group based on an intention-to-treat analysis. This patient allocated to HFMG incorrectly received SNC and required a higher flow of supplemental oxygen to complete their procedure. Only three patients in the SNC group required a change in the method of oxygen delivery. Two of these patients received a short period of bag-valve-mask ventilation, and a third patient received supplemental oxygen *via* a facemask for a brief period, before completing their upper GI endoscopies on higher flows of supplemental oxygen either *via* SNC or HFNC. No patients required intubation in the study. With regards to airway manoeuvres, a greater proportion of patients in the SNC group (42.9%) required a chin lift and/or jaw thrust manoeuvres compared to those in the HFMG group (17.4%) (*P* value < 0.001).

A total of 7 intraprocedural-related adverse events occurred, the endoscope was either withdrawn and re-inserted or the procedure paused in response to an episode of hypoxaemia or as directed by the duty anaesthetist. Only one of these patients was allocated to HFMG. No procedure-related or post-procedure complications were observed in the study. Sedation-related adverse events were infrequent and observed in ten patients (3.4%). These include hypotension, bradycardia, tachycardia, nausea and vomiting. One patient with hypotension in the HFMG group required two doses of 0.5mg dose of metaraminol. In the SNC group, one patient had bradycardia requiring a dose of atropine for bradycardia and two others received rescue antiemetics.

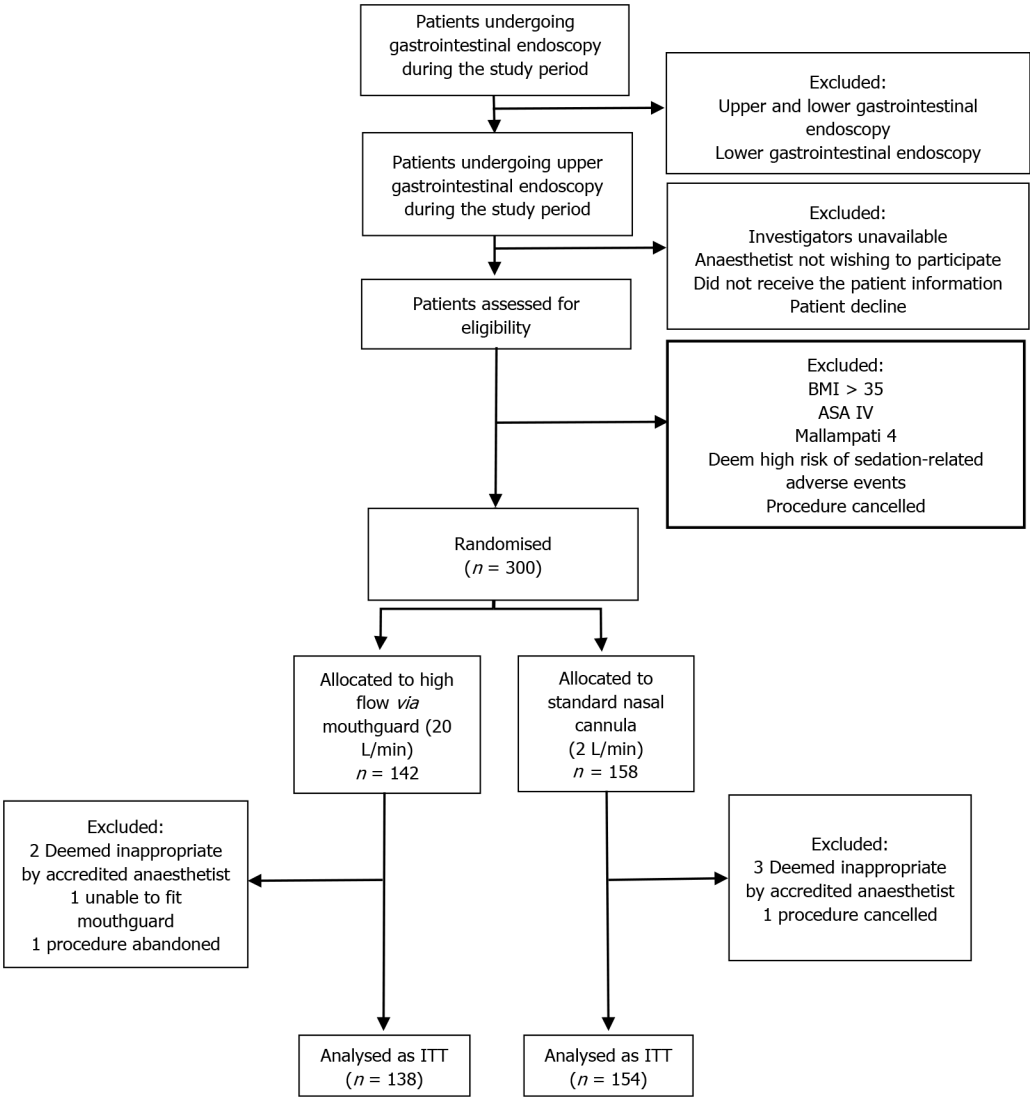

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Figure 2 Study flow chart. BMI: Body mass index; ASA: American Society of Anesthesiologists; ITT: Intention-to-treat; GI: Gastrointestinal.

No statistically significant difference in patient-reported symptoms was demonstrated. Patient-reported symptoms forms were completed by 74.3% of patients and no statistically significant difference in response rate was found between the two groups (Table 5).

DISCUSSION

In this single centre, randomised controlled trial, HFMG at 20 L/min of supplemental oxygen significantly reduced the incidence of hypoxaemia, defined as SpO_2 < 90% of any duration, when compared to SNC at 2 L/min of supplemental oxygen in patients undergoing elective upper GI endoscopy under deep sedation. Further, clinically significant hypoxaemia events were significantly reduced in patients assigned to HFMG compared to SNC. No statistically significant difference in patient-rated outcomes was observed between the two groups. To the best of our knowledge, this is the first study comparing the use of supplemental oxygen at 20 L/min *via* a commercially available mouthguard to 2 L/min *via* a standard nasal cannula.

Though further studies are required to elucidate the mechanisms by which HFMG reduces the incidence of hypoxaemia in patients undergoing upper GI endoscopy, we postulate that oxygen delivery into the oral cavity has additional benefits. During upper GI endoscopy, an open-mouth respiratory system, the oropharyngeal cavity serves as a large oxygen reservoir.[19] As such, we hypothesize that higher flows delivered into both the nasal and oral cavities result in higher FiO_2 delivery, greater physiological dead space washout, and positive end-expiratory pressure similar to that seen in HFNC[1].

Table 5 Patient-reported outcomes for the intention-to-treat analysis (*n*, %)

Patient-reported outcomes – Likert scale	SNC (*n* = 154)	HFMG (*n* = 138)	*P* value
(1 = Very uncomfortable or unbearable, 5 = Very comfortable or not at all)			
Response rate	115, 74.7%	102, 73.9%	0.882
Comfort level ≤ 2	4, 3.5%	5, 4.9%	0.6
Abdominal pain ≤ 2	3, 2.6%	0, 0.0%	0.1
Bloating ≤ 2	1, 0.9%	1, 1.0%	0.932
Mouth dryness ≤ 2	2, 1.7%	1, 1.0%	0.633
Mouth pain ≤ 2	2, 1.7%	1, 1.0%	0.633
Headache ≤ 2	1, 0.9%	1, 1.0%	0.932

HFMG: High flow *via* oxygenating mouthguard; SNC: Standard nasal cannula.

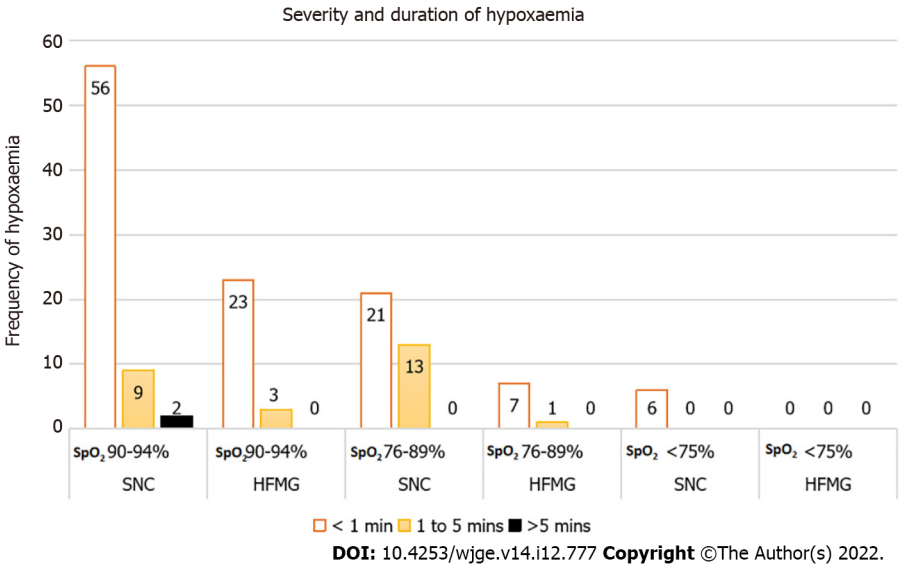

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Figure 3 Frequency and distribution of hypoxaemia. HFMG: High-flow *via* oxygenating mouthguard; SpO_2: Oxygen saturation; SNC: Standard nasal cannula.

Most importantly, we acknowledge the criticisms of choosing an oxygen flow rate of 2 L/min[11]. At the conception of the study, this decision was to allow inferences between HFMG and HFNC based on a recent publication by Lin *et al*[7]. In our study, of those allocated to HFMG, five patients (3.6%) experienced hypoxaemia and only one patient (0.7%) experienced an episode of severe hypoxaemia, as defined by Lin *et al*[7], respectively. Compared to HFNC, HFMG offers a relatively inexpensive and simpler method of delivering higher flows of supplemental oxygen. A single-use disposable mouthguard (Oxyguard™) with a rubber strap is approximately 2.33 USD. However, we acknowledge that further comparative studies are required to determine the cost-effectiveness of HFMG in upper GI endoscopy compared to HFNC and other airway devices.

Furthermore, this study has limitations. Firstly, we recognise that this is a single-centre study, and therefore further multicentre trials are required to validate our findings. Secondly, it is unclear whether a lower flow of supplemental oxygen would achieve the same observed benefits, and thus additional studies using different flows through this mouthguard would be warranted. Thirdly, procedures anticipated to be longer than 20 minutes, emergent or combined with a lower GI procedure were excluded. Further studies in these clinical scenarios are required. Finally, an adequate mouth opening is required to accommodate the 60Fr mouthguard. One patient allocated to HFMG did not have sufficient mouth opening which was only evident after randomisation. Although a smaller version of the Oxyguard™ is commercially available, this is not available at our centre. Studies using the miniature version of the mouthguard (Oxyguard™ mini; North Yorkshire, England) would be required to determine its clinical efficacy.

Concerning the use of pulse oximetry as our primary outcome measure, we appreciate its limitations relative to capnography[20]. Pulse oximetry is routinely used in all patients, and offers an objective and practical outcome measure. A strength of our study is the use of clinically significant hypoxemic events, as this encapsulates the anaesthetist's clinical assessment and interpretation of an episode of hypoxaemia and thus is a more clinically relevant outcome.

CONCLUSION

The use of high-flow supplemental oxygen *via* a mouthguard offers a simple and novel approach to reducing the incidence of hypoxaemia during short upper GI endoscopy in low-risk patients undergoing propofol sedation.

ARTICLE HIGHLIGHTS

Research background

Anaesthetic care during upper gastrointestinal (GI) endoscopy has the unique challenges of balancing adequate patient sedation while maintaining sufficient ventilation and oxygenation *via* a shared upper airway. Supplementary oxygen during upper GI endoscopy under deep sedation is considered the standard practice to reduce the incidence and severity of hypoxaemia. However, despite this being a recommendation of international society guidelines, the optimal route or rate of oxygen delivery is not known.

Research motivation

Various oxygen delivery devices have been investigated to improve oxygenation during upper GI endoscopy, however, these are limited by commercial availability, costs and in some cases, the expertise required for insertion. Anecdotally at our centre, higher flows of supplemental oxygen can safely be delivered *via* an oxygenating mouthguard. This oxygenating mouthguard is routinely used during upper GI endoscopic procedures in our practice and as such offers a practical solution to reducing the incidence and severity of hypoxaemia in patients undergoing upper GI endoscopic procedures under deep sedation.

Research objectives

To assess the incidence of hypoxaemia (SpO_2 < 90%) in patients undergoing upper GI endoscopy receiving supplemental oxygen using an oxygenating mouthguard at 20 L/min flow compared to standard nasal cannula (SNC) at 2 L/min flow as a proof-of-concept study.

Research methods

A single centre, prospective, randomised clinical trial at two sites of an Australian tertiary hospital between October 2020 and September 2021 was conducted. Patients undergoing elective upper gastrointestinal endoscopy under deep sedation were randomised to receive supplemental oxygen *via* high-flow *via* oxygenating mouthguard (HFMG) at 20 L/min flow or SNC at 2 L/min flow. The primary outcome was the incidence of hypoxaemia of any duration measured by pulse oximetry. Intraprocedural-related, procedural-related, and sedation-related adverse events and patient-reported outcomes were also recorded.

Research results

Three hundred patients were randomised. Eight patients were excluded after randomisation. 292 patients were included in the intention-to-treat analysis. The incidence of hypoxemia was significantly reduced in those allocated HFMG. Six patients (4.4%) allocated to HFMG experienced an episode of hypoxaemia, compared to thirty-four (22.1%) patients allocated to SNC (P value < 0.001). No significant difference was observed in the rates of adverse events or patient-reported outcome measures.

Research conclusions

The use of HFMG offers a novel approach to reducing the incidence of hypoxaemia during short upper gastrointestinal endoscopic procedures in low-risk patients undergoing deep sedation.

Research perspectives

Additional studies using different flows through the oxygenating mouthguard would be warranted to elucidate the mechanisms by which HFMG reduces the incidence of hypoxaemia in patients undergoing upper GI endoscopy. Further comparative studies are required to determine the cost-effectiveness of HFMG in upper GI endoscopy compared to high-flow nasal cannula and other airway devices.

FOOTNOTES

Author contributions: Be KH, Zorron Cheng Tao Pu L, Peyton P, Efthymiou M, Vaughan R, and Chandran S conceptualized and designed the study; all authors were involved in data collection, analyses, or both; all authors were involved in the interpretation of the results; Be KH, Zorron Cheng Tao Pu L, Lee M, Fletcher L and Chandran S drafted the manuscript; Pearce B, Cogan R, Efthymiou M, and Vaughan R carried the critical revision of the article for important intellectual content; and all authors read and approved the final version of the manuscript.

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Clinical trial registration statement: This study is registered at ANZCTR.org.au. The registration identification number is ACTRN12620000930987.

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CASE REPORT

Colonic schistosomiasis: A case report

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Abstract

BACKGROUND

Schistosomiasis is a chronic parasitic infection endemic in many countries. Colonic schistosomiasis is a rare entity with no specific clinical manifestations or endoscopic aspects, which delays the diagnosis. Diagnosis is primarily dependent on histopathological analysis, and treatment with antihelminthics typically resolves the infection.

CASE SUMMARY

We present the case of a 21-year-old male who suffered from chronic diarrhea and abdominal pain. Physical examination found no abnormalities, blood tests were normal, and stool examination was negative. A colonoscopy revealed a nodular terminal ileal mucosa, two cecal polypoid lesions with no particular surface pattern, and millimetric erosions in the rectum. The presence of *Schistosoma* eggs with thick peripheral capsules and viable embryos inside and numerous eosinophils surrounding the egg capsule were observed on histopathological examination. The patient received praziquantel, and his symptoms were resolved.

CONCLUSION

Colonic schistosomiasis should be considered as a differential diagnosis, especially in endemic countries. Endoscopy and histopathological examination can confirm the diagnosis, and antihelminthics are an effective treatment.

Key Words: *Schistosoma*; Colon; Polyps; Colonoscopy; Histopathology; Ova

Core Tip: Colonic schistosomiasis is a rare disease, often mistaken for other pathologies, such as inflammatory bowel disease, because the clinical and endoscopic manifestations are non-specific and can be misleading. Histopathological examination is key to diagnosis when the stool examination shows no ova. We present a case of colonic schistosomiasis in a 21-year-old male presenting with chronic diarrhea and abdominal pain. The stool examination was negative and colposcopy showed multiple polyps. Histopathological examination confirmed the diagnosis of colonic schistosomiasis. Antiparasitic treatment was effective.

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INTRODUCTION

Schistosomiasis is a serious chronic parasitic infection caused by trematodes, primarily *Schistosoma mansoni* and *Schistosoma japonicum*. Humans are accidental hosts; infection occurs after ingesting larva-infested water. According to the World Health Organization, 236.6 million people needed preventative treatment in 2019 and the global death rate ranged between 24000 and 200000. *Schistosoma* commonly infects the urinary tract, and intestinal infection is rare. Its clinical manifestations are non-specific, ranging from asymptomatic to intestinal occlusion secondary to larva deposits, diarrhea, abdominal pain, malnutrition, and chronic anemia. Colonoscopy can reveal lesions, among which mucosal edema, ulcerations, and polypoid lesions are frequently observed[1].

Herein, we present a case of a 21-year-old male with colonic schistosomiasis.

CASE PRESENTATION

Chief complaints

A 21-year-old male, originally from Madagascar but living in Morocco for the past 5 years, presented with chronic diarrhea up to 3-4 times a day, diffuse abdominal pain prominent to the right iliac fossa and intermittent subocclusive symptoms for 3 years with no recent aggravation.

History of present illness

The patient suffered from his complaints for 3 years prior to presentation, and they occurred in a flare-up/remission pattern.

Physical examination

The physical examination found no abnormalities. The patient had a normal body mass index. No abdominal tenderness nor mass was noted.

Laboratory examinations

Blood tests gave normal findings, showing negativity for C-reactive protein levels. Stool examination for parasite ova and bacterial culture were negative.

Imaging examinations

A thoracic abdominopelvic computed tomography scan revealed no abnormalities.

ENDOSCOPIC EXAMINATION

Colonoscopy revealed a nodular terminal ileal mucosa, two cecal polypoid lesions with no particular surface pattern, and millimetric erosions in the rectum (Figure 1A). Biopsies were taken with jumbo forceps. Histopathological examination showed the presence of *Schistosoma* eggs with thick peripheral capsules and viable embryos inside (Figure 1B). The egg capsules were surrounded by numerous eosinophils (Figure 1C).

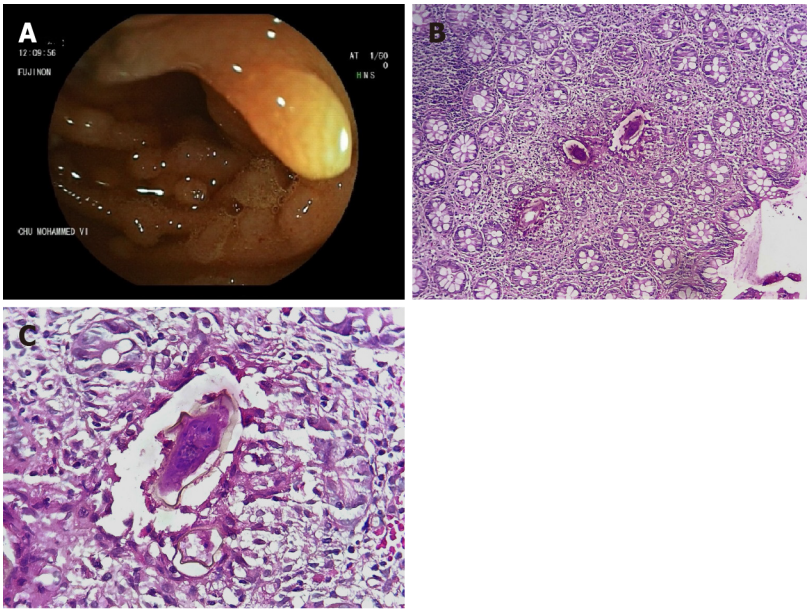

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Figure 1 Colonoscopy and histopathological findings. A: Polyps were observed during colonoscopy; B: Microphotography showed the presence of three *Schistosoma* eggs in the colic mucosa (hematoxylin and eosin, × 40); C: Microphotography of a *Schistosoma* egg showed a thick peripheral capsule and a viable embryo inside. The egg capsule was surrounded by numerous eosinophils (hematoxylin and eosin, × 400).

FINAL DIAGNOSIS

Colonic schistosomiasis.

TREATMENT

The patient received praziquantel (60 mg/kg in two doses over a 1-d period).

OUTCOME AND FOLLOW-UP

The treatment resolved the diarrhea and alleviated the abdominal pain.

DISCUSSION

Schistosomiasis, also known as Bilharzia, is a parasitic infectious disease caused by schistosomes. Its geographical distribution is widespread, with endemic foci in some regions of the world (Africa, South America and Asia). *S. mansoni* and *S. japonicum* are typically involved in digestive schistosomiasis. In Africa, colonic polyposis is generally associated with *S. mansoni* infection[2]. Patients are infected after direct contact with water contaminated with snails carrying the parasite. The urinary system is preferentially affected, while intestinal involvement is rare.

Symptoms can be non-specific, and the evolution of the infection can last for long periods (as reported in our case). Diarrhea is the main symptom, as 3%-55% of a population study presented with diarrhea, with 11%-50% of cases presenting with bloody diarrhea[1]. In a study of 216 patients with intestinal schistomiasis, by Mohamed *et al*[2], abdominal pain and diarrhea were the most frequent symptoms, accounting for 39 % and 27% of cases respectively. In another study by Rocha *et al*[3], diarrhea was also the most common symptom, observed in 56% of cases. Abdominal pain, constipation, weight loss and fatigue are commonly observed, while obstructive symptoms, such as intestinal stenosis, are rare.

Differential diagnosis with inflammatory bowel disease and malignancy can be challenging. Hypereosinophelia is a nonspecific finding of schistomiasis correlating to the stage, intensity, and duration of infection. Stool examination may reveal ova, which is essential in determining larva species [1,2]. However, detecting ova in the stool can be difficult, as the numbers decrease as the infection evolves. Quantitative sampling according to the Kato-Katz technique coupled with concentration

technique improves the sensitivity of egg detection; the diagnosis sensitivity could also be improved by associating Kato-Katz sampling examination with serological testing (*e.g.*, IgG anti-*Schistosoma mansoni*-enzyme-linked immunosorbent assay technique)[4]. Serological diagnosis by detection of serum antibody titer is also available, especially in endemic areas, but it cannot differentiate between active or chronic infection; meanwhile, a negative serological test can rule out infection in endemic areas but cannot be used in post-treatment follow-up due to prolonged positivity post-therapy[5]. Detection of free circulating DNA by polymerase chain reaction can be used for early diagnosis of prepatent schistosomiasis infection[6], with good sensitivity and specificity for urine samples (94.4% and 99.9% respectively)[7]. Serologic tests for the detection of one of the two gut-associated parasite proteins ¾ circulating anodic antigen and circulating cathodic antigen ¾ can also be used for diagnosis[8].

When digestive colonization occurs, superficial submucosal deposits of *Schistosoma* eggs lead to the formation of polypoid lesions corresponding to inflammatory granulation tissue and hypertrophy of the adjacent muscular layer. Colonoscopy can show polypoid lesions, edema, ulcers, and granular patterns [9-13]. In the study mentioned above by Mohamed *et al*[2], polyps were found in only 8 cases (3 were rectal and 5 were colonic), and histopathological examination showed schistosomal ova in all 8 of the polyps. Cao *et al*[10] observed that nodular lesions and polyps are more frequent in the left colon, while mucosal edema, erythema, granular pattern, and ulcers are often seen in the right colon. In this study, 4 patients were misdiagnosed as ulcerative colitis, 1 as Crohn's disease, and 7 as ischemic colitis. While intestinal lesions associated with *S. mansoni* are usually observed in the ileum and the colon, duodenal involvement has been reported as well. Based upon visualization of schistosomal ova, biopsies and histopathological examination are the golden diagnostic standard of colonic schistomiasis. The ova are mainly deposited in the lamina propria and/or submucosa[11], with an observable inflammatory reaction in the tissue surrounding them[10,12]. Other characteristic features are excessive mucus and diffuse or focal infiltration of eosinophilic granulocytes, which may be highly suggestive of colonic schistosomiasis[14], as seen in our patient. In addition, intestinal ultrasound and computed tomography may reveal wall thickening, but they show no abnormalities in most cases. Abdominal X-rays and barium enemas can show images of polyps and structures but are not typically utilized due to their lack of specificity.

Intestinal schistosomiasis is amenable to medical treatment, including praziquantel, with a safe and effective outcome and cure rates ranging between 60% and 90%[15]. It has been shown that antigen tests become negative as early as 5-10 d after successful therapy[16]. A study from Africa that aimed to evaluate the efficacy and safety of praziquantel in preschool-aged children in an area co-endemic for *Schistosoma* concluded the efficacy of crushed praziquantel administered to preschool-aged children at a dose of 40 mg/kg against *S. mansoni* and *Schistosoma haematobium*[17]. Mutapi *et al*[18] had also concluded from their study that praziquantel is safe and efficacious in children aged 1-10 years.

Praziquantel is substantially excreted by the kidney, and elderly patients with decreased renal function may be at greater risk of toxic reactions. In a study conducted by Putri *et al*[19], the group aged 45 to 69 experienced a high proportion of side effects.

A second praziquantel regimen can be prescribed in case of persistence of the infection; oxamniquine alone or combinated with praziquantel and trioxolane can also be used as second-line therapy.

Following treatment, stool analysis or colon biopsy could be considered for assessment of treatment success but should be performed at least 6 wk post-treatment[20]. No data are available in the literature regarding colonic polyps' endoscopic follow-up and monitoring.

Cases of colon cancer associated with *S. japonicum* have been reported. However, the carcinogenic pathways are unclear, and the association is not well established[2,10,21]. A Chinese study including 454 colorectal carcinoma specimens showed that more than half (n = 289) were associated with *S japonicum* infection[22]. Furthermore, a study by Kaw *et al*[23] including 1277 colonic carcinoma patients showed that schistosomiasis was often accompanied by rectal cancer.

Schistosomiasis prevention is key to its elimination; public health awareness campaigns, water sanitation, hygiene programs, and chemotherapy programs are necessary. Preventive chemotherapy in preschool-aged children is deemed appropriate for those aged ≥ 2 years in endemic communities, according to the World Health Organization. While an antischistosomal vaccine will be ideal for long-term protection, clinical trials for its development are still in progress.

CONCLUSION

Colonic schistosomiasis is a rare disease that should be considered a differential diagnosis in endemic regions. Endoscopic appearance is non-specific. Histopathological and stool examinations have a significant role in diagnosis.

FOOTNOTES

Author contributions: Koulali H, Zazour A, Khannoussi W, Kharrasse G, and Ismaili Z participated in collecting and analyzing the patient's data and designing the report.

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