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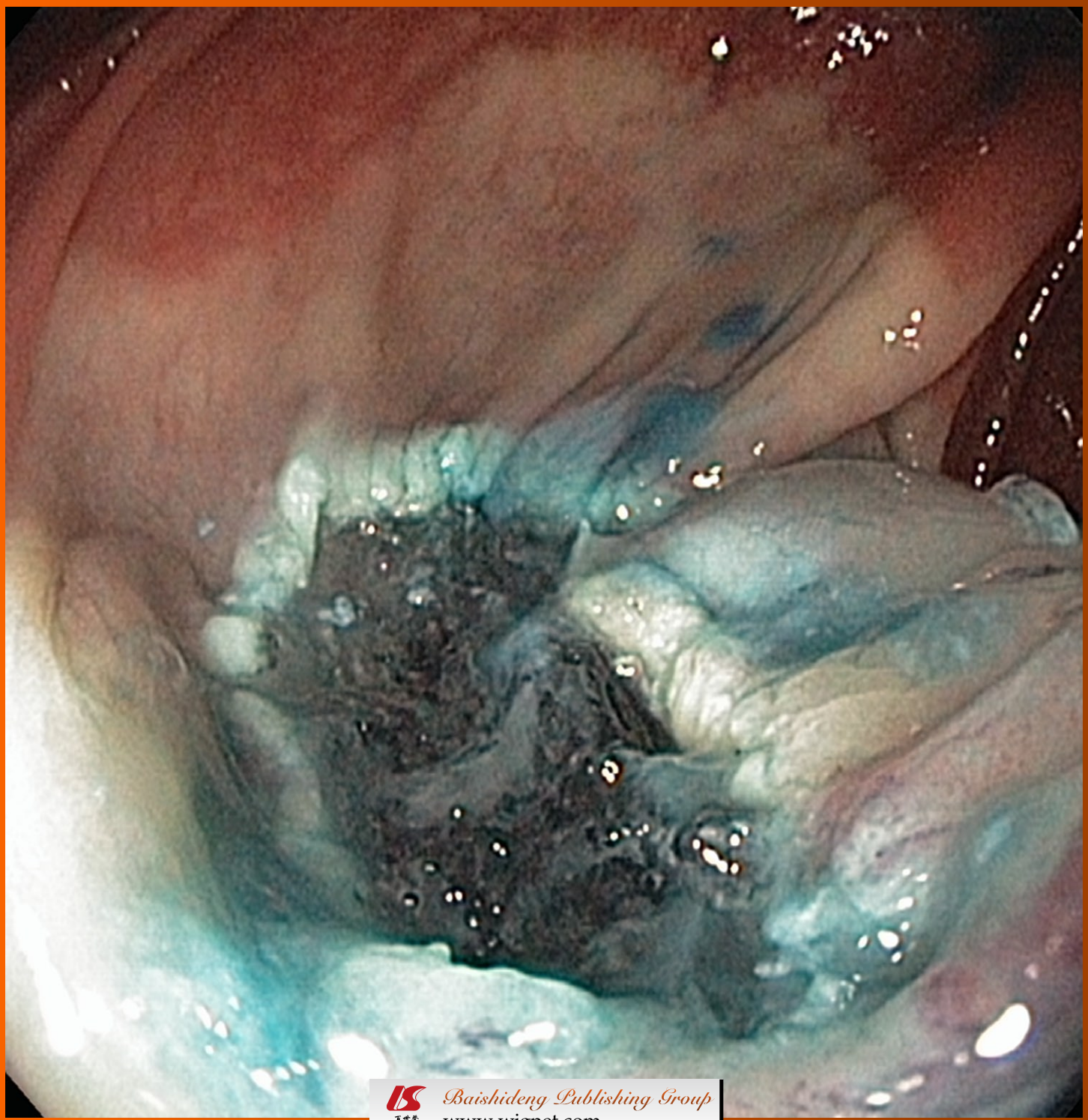

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EDITORIAL

Difficult colon polypectomy

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Abstract

Colorectal cancer (CRC) is one of the leading causes of death from cancer in the world. We now know that 90% of CRC develop from adenomatous polyps. Polypectomy of colon adenomas leads to a significant reduction in the incidence of CRC. At present most of the polyps are removed endoscopically. The vast majority of colorectal polyps identified at colonoscopy are small and do not pose a significant challenge for resection to an appropriately trained and skilled endoscopist. Advanced polypectomy techniques are intended for the removal of difficult colon polyps. We have defined a "difficult polyp" as any lesion that due to its size, shape or location represents a challenge for the colonoscopist to remove. Although many "difficult polyps" will be an easy target for the advanced endoscopist, polyps that are larger than 15 mm, have a large pedicle, are flat and extended, are difficult to see or are located in the cecum or any angulated portion of the colon should be always considered difficult. Although very successful, advanced resection techniques can potentially cause serious, even life-threatening complications. Moreover, post polypectomy complications are more common in the presence of difficult polyps. Therefore, any endoscopist attempting advanced polypectomy techniques should be adequately supervised by an expert or have an excellent training in interventional endoscopy. This review describes several useful tips and tricks to deal with difficult polyps.

Key words: Colonoscopy; Polypectomy; Mucosectomy; Colon polyp; Polyp; Endoscopic mucosal resection; Mucosectomy; Endoscopic submucosal dissection

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INTRODUCTION

Colorectal cancer (CRC) is one of the leading causes of death from cancer in the world. We now know that 90% of CRC develop from adenomatous polyps[1]. Polypectomy of colon adenomas leads to a significant reduction in the incidence of CRC[1,2]. At present most of the polyps are removed endoscopically[2-5]. The vast majority of colorectal polyps identified at colonoscopy are small and do not pose a significant challenge for resection

to an appropriately trained and skilled endoscopist[2-4]. Advanced polypectomy techniques are intended for the removal of difficult colon polyps. We have defined a "difficult colon polyp" as any polyp that due to its size, shape or location makes it difficult for the colonoscopist to remove[3]. Although many "difficult polyps" will be an easy target for the advanced endoscopist, polyps that are larger than 15 mm, have a large pedicle, and are flat and/or laterally spreading, are difficult to see or are located in the cecum or any angulated portion of the colon should be always considered difficult[3-7]. Although very successful, advanced resection techniques can potentially cause serious, even life-threatening complications[4-6]. Moreover, post polypectomy complications are more common in the presence of difficult polyps[5,6]. Therefore, any endoscopist attempting advanced polypectomy techniques should be adequately supervised by an expert or have an excellent training in interventional endoscopy. This review describes several useful tips and tricks to deal with difficult polyps.

PATIENT PREPARATION

The patient should undergo a detailed preoperative history and physical examination. The physician must inform the patient about the benefits and risks of colonoscopy and endoscopic polypectomy, including the risk of missing lesions and the risk of sedation. Routine preoperative laboratory blood testing is not indicated before polypectomy[3,4,8,9]. Blood testing should be done in patients suspected of harbouring a blood dyscrasia and those who are being treated with oral anticoagulants or heparin and its derivates[8]. Although there are limited data sowing no increased risk of bleeding after polypectomy in patients taking nonsteroidal antiinflammatory drugs, aspirin or clopidogrel, most endoscopists ask the patient to stop these medications seven days before polypectomy[3,4,8,9]. A prerequisite for advanced polypectomy is an adequate bowel preparation. A clean bowel may prevent the development of an overwhelming peritonitis and sepsis should a perforation occur. The aim should be to perform advanced polypectomy only if the colon preparation reaches a Boston scale 2 or 3[10]. If the colon is inadequately prepared, we recommend repeating the procedure on another occasion. It is better to be safe than sorry!

DIFFICULT COLON POLYPS AND THEIR ENDOSCOPIC APPROACH

A difficult polyp is any flat or raised colonic mucosal lesion that due to its size, shape and location makes it difficult to remove[3,4,7,9] (Table 1) (Figures 1-5). Even the number of polyps might be considered a "difficult polypectomy" as the rate of significant complications increases with the number and complexity of polypectomies[3-6,11]. Polyp removal should follow a standardized approach. All the equipment and accessories employed for polypectomy should be readily available. Table 2 lists common accessories utilized during advanced polypectomy. We have a special cabinet in every room containing snares, needles, clips, endoloops and the material needed for submucosal cushion injection[12-16].

STEPS TO FOLLOW WHEN CONFRONTED WITH A DIFFICULT POLYP

There are eight important steps to follow, which should lead to a successful colon polyp resection, especially when confronted with difficult polyps. These are enumerated in Table 3 and will be discussed in subsequent order below. Table 4 lists some basic principles, tips and tricks when dealing with difficult colon polyps.

Location of the polyp

First, the location of the lesion shall be noted. Is the polyp located in the right or left colon? Because of the thinness of the wall, anatomically the ascending colon, the cecum and the descending colon are the most dangerous sides for polypectomy, especially when much air is insufflated. Polyps located in these locations should be treated with additional caution[3,4]. If the polyp is located in the dorsal or retroperitoneum side of the body, minor perforation may be managed conservatively. Thus it can be useful to change the patient's position before the endoscopic treatment to confirm the site of the polyp. Polyps located in the rectum are prone to bleed more during or after resection, as the vascular supply to this area is very rich.

When using submucosal injection solutions with vasoconstrictors (i.e., adrenaline) or hypertonic mixtures are mandatory[3,4,9]. Taking out the air will also decrease tension on the wall, allow for better ensnaring of the polyp and increase the thickness of the underlying submucosal and muscular layers. When the polyp has been grasped it is imperative to create a "tent". By doing so, the electrosurgical current will tend to remain at the proximal base of the polyp, decreasing the pressure of the snare (and hence electrical current) against the colon wall[4]. The endoscopist should also evaluate the relation of the polyp to the colonic folds (Figure 1). Polyps on top of folds should be always raised with a submucosal cushion as grabbing too much tissue with a snare could result in deep resection lesions leading to perforation. Also, larger polyps lying between two folds or extending beyond two folds shall always be removed using submucosal cushion and either piecemeal endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) (see separate sections on submucosal cushion, EMR and ESD)[3-6].

Analyze the polyp's shape

Although there is no foolproof method to categorically best define a lesion endoscopically, the most commonly used categorization is the Kyoto-Paris classification of gastrointestinal neoplasia[7]. It differentiates a type I protruding lesion (pedunculated, sessile), from a type Ⅱ

Table 1 Defintion of difficult colon polyp

Shape (morphology)	Flat or hard to see
	Sessile > 15 mm
	Carpet shaped (laterally spreading tumor)
	Villous or granular
	Irregular surface, irregular pit pattern, villous or granular
	If pedunculated, thick or short pedicle
Size	< 1.5 cm
	Large > 3 cm
	Big head
Number	Multiple (> 3)
Location	Right colon and cecum
	Ileocecal valve
	Appendix orifice
	On top or behind of folds
	Difficult endoscopic position

Table 2 Nine steps leading to a successful polypectomy

Locate of the polyp
Analyze the polyp's shape
Determine the polyp's size
Analysis of the polyp surface
Determine the number of polyps
Position the polyp before attempting its resection
Estimate polyp respectability using endoscopic methods
Use the submucosal cushion (injection-assisted-polypectomy)
Appropriate skills using clips and/or endoloops

non-protruding, non-excavated lesion (slightly elevated, completely flat, slightly depressed) and excavated type Ⅲ lesion[7]. However, this classification applies to all lesions of the entire gastrointestinal tract, including squamous and cylindrical mucosal neoplasia. The astute reader will notice that the Kyoto-Paris classification refers to "non-polypoid" lesions, i.e. it excludes sessile and pedunculated polyps. Thus, we prefer to call a polyp what it is (i.e., a polyp) and avoid complex terminology that can lead to more confusion. Moreover, this classification calls these "non-polypoid" structures "lesions" and in addition it also classifies many non-polypoid lesions as polypoid, sessile or pedunculated. Thus, we try to remain practical and stick to a simple description of a colon polyp[3,4]. One can differentiate between a pedunculated polyp (polyps with a stalk, stem, pedicle or peduncle) (Figure 2) and those without a pedicle (i.e., sessile polyps)[3] (Figure 3). The third type is the flat lesion (Figures 1, 4 and 5). For a flat or sessile polyp it is important to determine their base surface and spreading appearance (i.e., lateral growth), their surface (nodular or villous or mixed) and whether they have a central depression or ulceration. Baptizing these lesions with Roman numbers and alphabetical letters may not lead to a better endoscopic resection! Lesions larger than 15 mm should be resected using adjunctive techniques such as submucosal cushion or piecemeal methods[3-6] (Figures 1, 6 and 7). Excellent knowledge of the existing accessories, electrosurgical devices and electrical currents (i.e., endocut, coagulation, pure cut, blend) used to resect and retrieve polyps and to prevent complications is mandatory[3,4,11-19] (Table 3). Pure cutting and "blended" currents result in more immediate bleeding, whereas coagulation currents result in more post-polypectomy bleeding and transmural perforation[16-19]. We prefer to use true blended currents (endocut) or pure cutting currents as immediate bleeding can be easily treated with clip application or injection. Endocut is a true blended current as a computer located in the electrosurgical unit determines it[17]. We do not use hot biopsy techniques to remove any polyp or polyp remnants as this technique can result in transmural burn, especially in the cecum. In addition, the histopatholgical specimen is often "burned"[19].

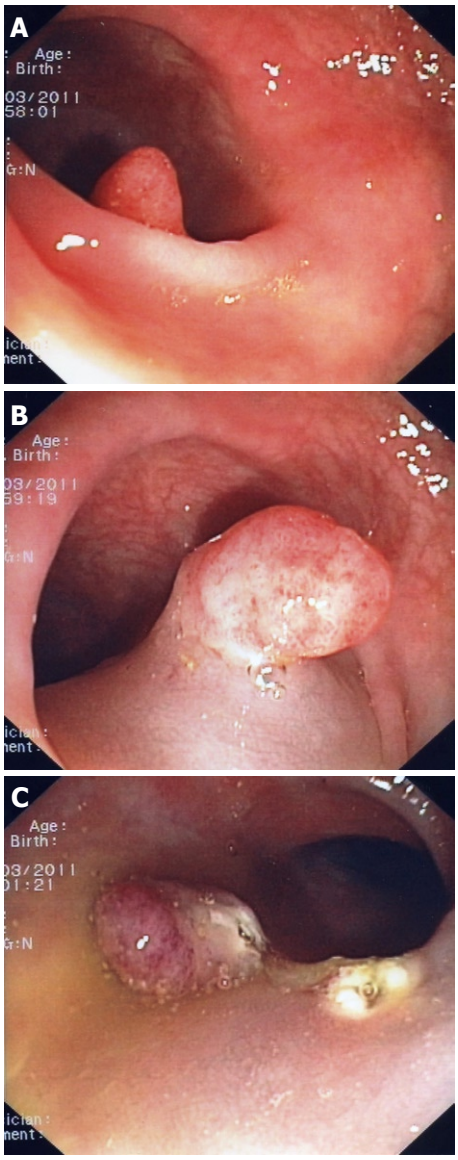

Figure 1 Difficult polyp located "behind" a fold (A). A closer look indicates that this is a large sessile polyp (B). The polyp was resected using mucosectomy technique (C).

Determine the polyp's size

There is no clear-cut definition for "large polyp". However, polyps > 20 mm should be considered "large", >

Table 3 Accessories and utensils used in advanced polypectomy

Hot biopsy forceps (we do not recommend to use hot biopsy forceps for colon polyp removal)
Single use
Resusable
Monofilament and braided wire snares of various diameters, e.g. mini < 11 mm, standard 15-45 mm)
Mini oval (recommended to remove diminutive polyps using the cold-snare technique, i.e. without heat of electrosurgical current)
Standard oval
Hexagonal
Crescent
Spiral
Mini barbed (the multiple barbs (help hold the tissue inside of the snare)
Needle-tip anchored (the needle tip on top the distal part of the snare helps stabilize the position of the snare, however the tip can lacerate the healthy mucosa)
With heat- resistant net (Nakao net) (not widely available)
Injection needle(s)
Injection substances (normal saline, hypertonic saline, dextrose 50%, adrenaline, sodium hyaluronidate
India ink (used for tattooing and marking)
Dyes (methylene blue, indigo carmine)
Combination needle/snare (allows for injection-assisted polypectomy and immediate snaring)
Rotatable snares (may be useful for polyps located in difficult lumenal location, when the scope cannot be torqued to an ideal position)
Endoscopic fitted caps (allow the detection of polyp behind folds)
Without snare rim
With snare rim
Needle knifes (at least 20 different types available for endoscopic submucosal dissection)
Without insulated tip
With insulated tip
Flush-knife
Clips (hemoclips or endoclips) (single use or reusable)
Endoloops
Retrieval devices
Baskets
Nets (Roth net)
Grasping forceps with two to five prongs

40 mm very large and > 50 mm "giant" (Figures 6 and 7). Size alone does not neglect resectability. This will rather depend on polyp location (cecum versus left colon, see above) and degree of neoplasia (i.e., invasive cancer). The degree of neoplasia can be often determined by inspecting the polyp surface (see separate paragraph below). Ulcerated polyps and those with a deranged pit- and vascular pattern should not be resected unless the aim is to perform a debulking procedure. Furthermore, polyps larger than 20 mm should be dealt with more caution, especially if these are flat or sessile. For polyps with a pedicle the most important aspect is, whether the stalk is thin or a thick or short or long. The advanced endoscopist should always aim at achieving an oncologic resection, i.e. the entire specimen should be removed. Thus, flat, and most sessile lesions measuring > 15-20 mm should be resected after the creation of a submucosal cushion (see separate paragraph on submucosal cushion below). This will ensure a safer margin of resection, possible reduce complications such as perforation and

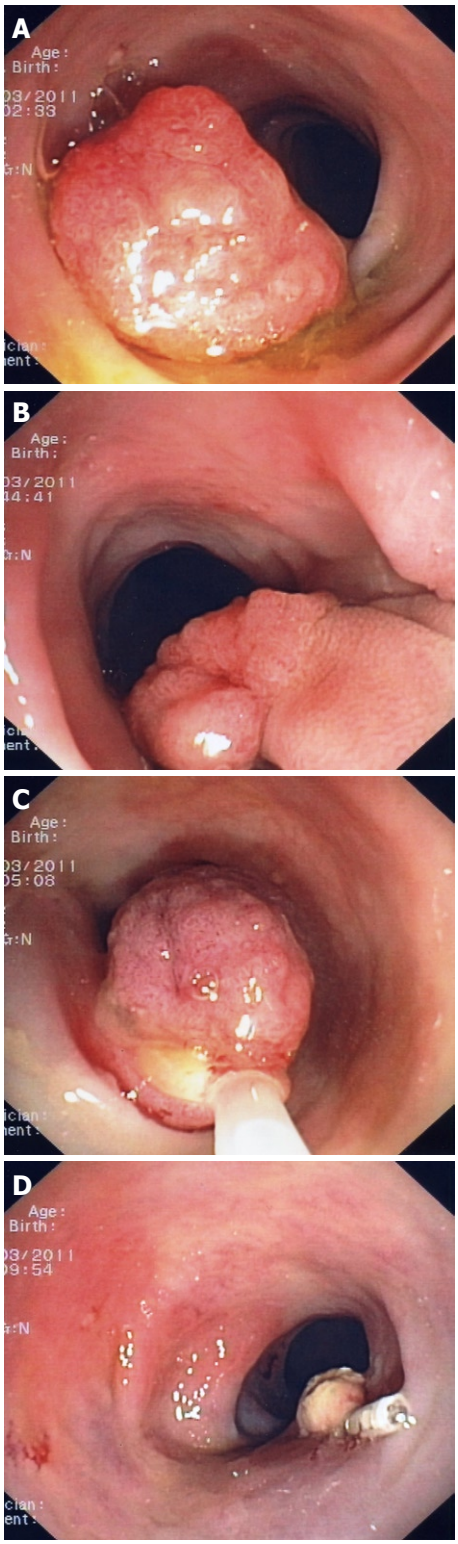

Figure 2 Large polyp located in the transverse colon (A). A closer inspection reveals that this polyp has a thick stalk (B); After injecting the stalk with adrenaline-saline mixture the snare was placed around it; Notice that the snare exits the scope at 5 o'clock position (C); A clip was placed at the base of the stalk to prevent post-polypectomy bleeding (D).

provide the pathologist with a good specimen to analyze. One of the most frustrating aspects of advanced colonoscopy is to send a specimen to the pathologist just to hear that the depth and lateral margins of the specimen

Table 4 Technical tips and tricks to improve the resection of difficult colon polpys

	Difficult polyps	Technical tips
Morphology	Sessile	Use submucosal cushion
	> 1 cm	Resect *in toto* (except cecum)
Size and form	< 1.5 cm	Use diluted epinephrine and Perform piecemeal resection, EMR or ESD
	Large (> 3 cm), on top of folds, carpet-like polyp or with villous or granular surface	
		Use APC for tissue remnants
	Big head	Use diluted epinephrine in head
	Pedunculated (if large)	Use clips or loops
	Thick pedicle	Use clips or loops
	Multiple	Send to pathologist separately
Number	Right colon and cecum	Do not use hot biopsy forceps
	Located behind folds	Inject distally first
Location	Difficult endoscope position	Change scope to 5 o'clock position
		Perform abdominal compression or change patient's position
		Use antispasmodic (e.g., butylscopolamine)
		Take air out before catching or snaring the polyp
		Resect when going in (if small) or when going out (if large)
	Increased colon motility	Mark the polyp site with India ink
General recommendations	Suspicious polyp or large, incompletely resected	
Abbreviations	APC	Argon plasma coagulation
	ESD	Endoscopic submucosal dissection
	EMR	Endoscopic mucosal resection

APC: Argon plasma coagulation; ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection.

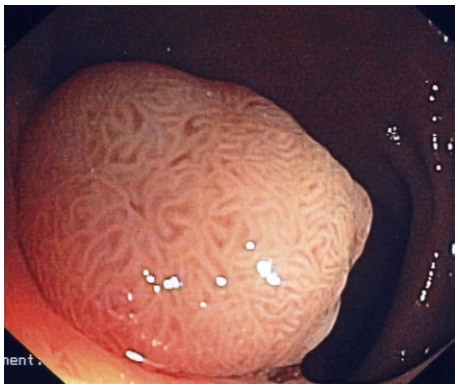

Figure 3 Large sessile polyp with cerebriform pit-pattern. This polyp was an adenoma with high-grade dysplasia.

could not be well seen due to cautery artefact and a superficial resection.

Analysis of the polyp surface

Make sure that the surface (pit-pattern) of the polyp is well investigated. Regular, cerebriform convolutions generally reflect an adenoma (Figure 3), whereas irregular, highly vascularised surface often indicates a carcinoma[7,20] (Figure 5). Whether the complex and constantly in evolution and modified pit-pattern classifications will help establish a clear-cut pre-operative diagnosis is still not clear[7,20]. We want to alert the advanced endoscopist that even polyps with a regular appearing surface can contain carcinoma! Furthermore, most hyperplastic-appearing lesions of the right colon are serrated adenomas or contain adenomatous elements and should thus be resected. In essence, and with the exception of submucosal lesions, we follow a policy of "I see and then resect". However, chromoendoscopy and magnification endoscopy can be useful to help us characterize colon polyps and the advanced endoscopist should master the principles of these techniques.

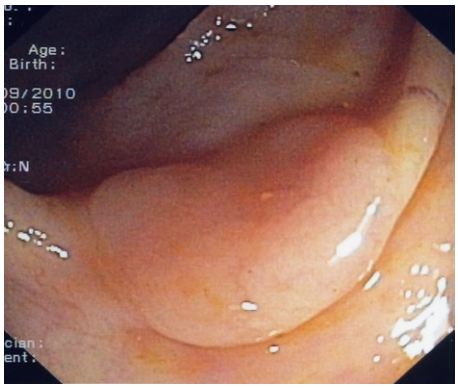

Figure 4 Typical flat polyp located on top of a fold.

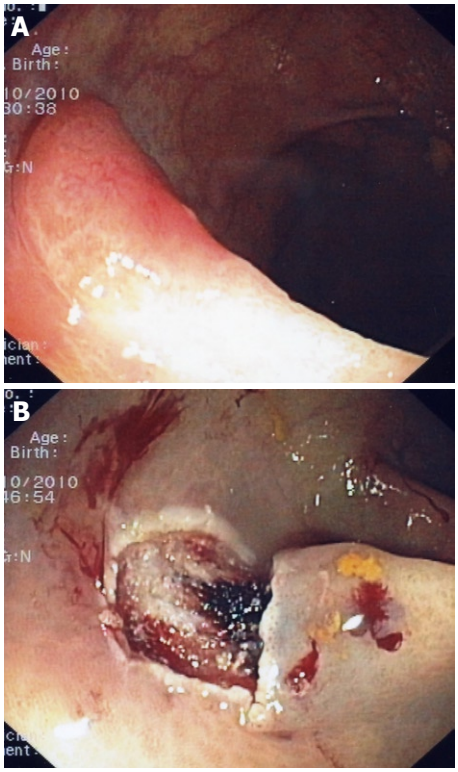

Figure 5 Flat polyp with irregular vascular pattern (A). Mucosectomy site (B); This polyp contained invasive cancer. A subsequent laparoscopic segmental section of the colon was performed.

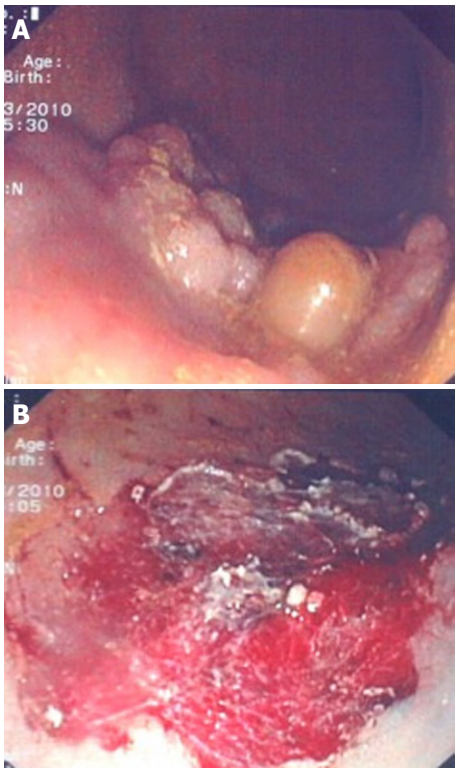

Figure 6 Large sessile polyp (A) and polyp site after performing piecemeal mucosectomy (B).

Today, we differentiate between virtual and real chromoendoscopy methods[20]. Standard chromoendoscopy techniques include contrast (e.g., indigo carmine) and vital dyes or stains (e.g., methylene blue)[20] (Figure 8). Virtual chromoendoscopy methods such as narrow band imaging, "Fujinon intelligent chromoendoscopy" or Fujinon-enhanced color enhancement (FICE) or I-Scan avoid the use of dye spray[20-22] (Figure 9). These methods allow enhancing the mucosal (pit pattern) and submucosal capillary network detail, both of which can be deranged in the presence of a neoplasia.

The results regarding polyp detection using virtual and/or standard chromoendoscopy are controversial[20-22]. However, the characterization of polyps can be enhanced using these methods. Nevertheless, the scant data available using the complex pit pattern or submucosal capillary pattern classifications do not support a crucial role of any chromoendoscopic method on the polypectomy-decision making process. The bottom line is that in practice we will not leave any polyp > 10 mm in situ just based on the pit pattern appearance. In addition, smaller polyps may also contain advance neoplasia or cancer. Whether a process of inspect, resect and discard based on a suspected endo-pathological diagnosis is worthwhile goes beyond the scope of this review paper which deals with advanced resection techniques for colon polyps[23].

Position of the polyp

The lumenal position of the polyp can be awkward and difficult its ensnarement. Always attempt to place the polyp at the 5 to 6 o'clock position, as this is the position were the snare and other accessories (e.g., needle, clips, *etc*.,) exit the scope. A useful rule is passing the scope far beyond the polyp, even as far as the cecum and then attempting capture during the withdrawal phase of the examination. Whenever a polyp is approached, snare placement is facilitated by rotation of the colonoscope, which brings the polyp in the 5 o'clock position[3,4]. An advantageous position may be best accomplished when the colonoscope shaft is straight, because a straight instrument transmits torque to the tip, whereas a loop in the shaft tends to absorb rotational motions applied to the scope. Other useful tips to improve polyp positioning are applying abdominal pressure and changing of the patient's position. In exceptional situations a good positioning is not possible. Still, a careful polypectomy

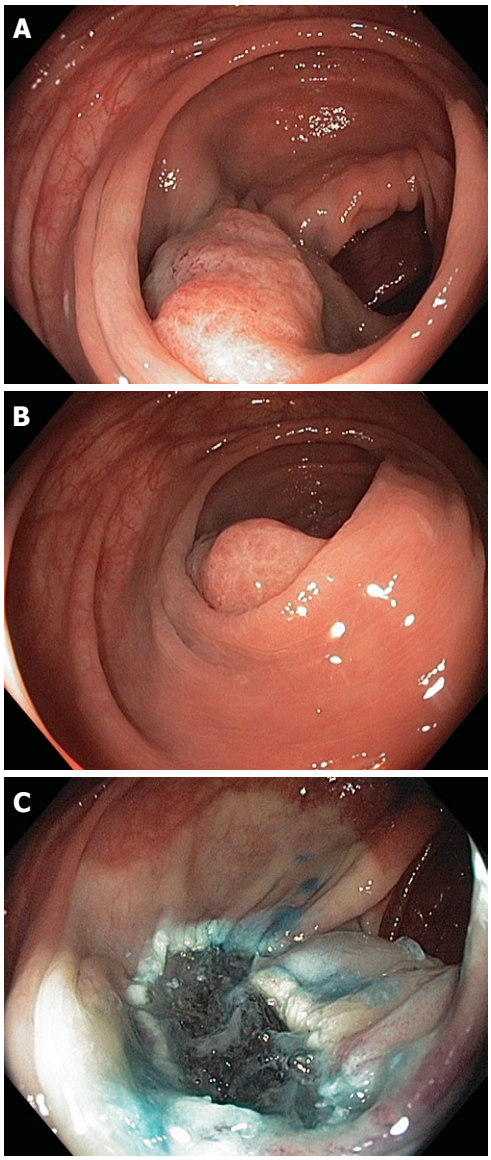

Figure 7 Sessile polyp located behind a fold (A), the creation of the submucosal cushion enabled the clear visualization of the polyp (B) and endoscopic resection site (C).

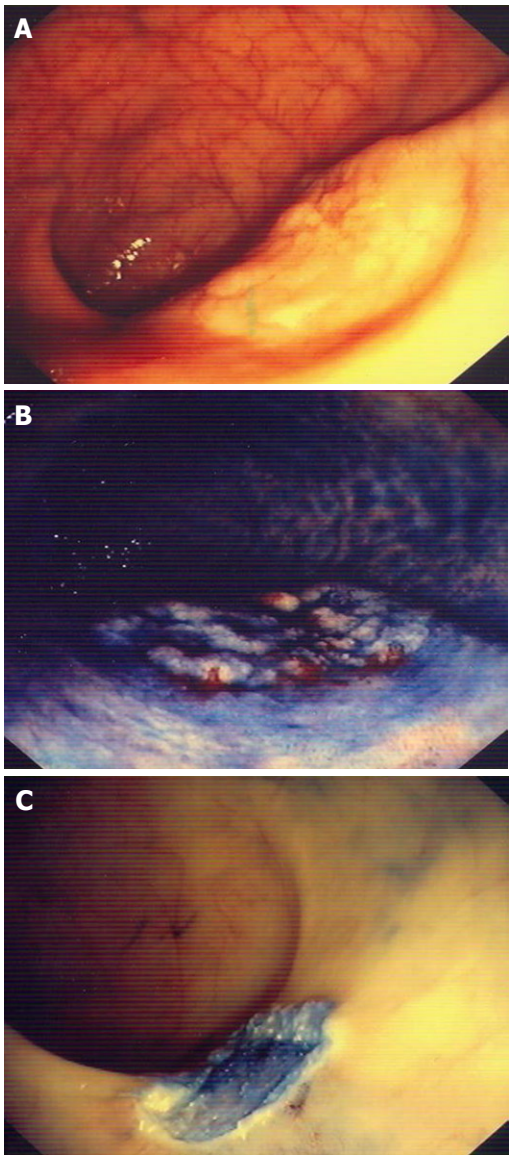

Figure 8 Flat polyp located in the rectum (A), demarcation of the polyp edges and surface with standard chromoendoscopy (indigo carmine) (B) and endoscopic mucosal resection site (C).

may be attempted while an assistant holds the scope in a stable position. Retroflexion is also a maneuver that can be carefully performed in any part of the colon and improve polypectomy success[24]. On the other hand changing scopes might be the best option (i.e., use a gastroscope, which has the opening of the accessory channel at the opposite position (7 o'clock position). Furthermore, utilizing the "double-scope" technique may result in a successful resection of complicated polyps[25,26].

Number of polyps

The number of colon polyps will determine the time and instruments to be used. If multiple polyps are present these and be collected as they are resected using a Roth's net[3,4]. But even small polyps can contain an invasive carcinoma and so the location of the polyp can't be transmitted to the pathologist. Some experts send

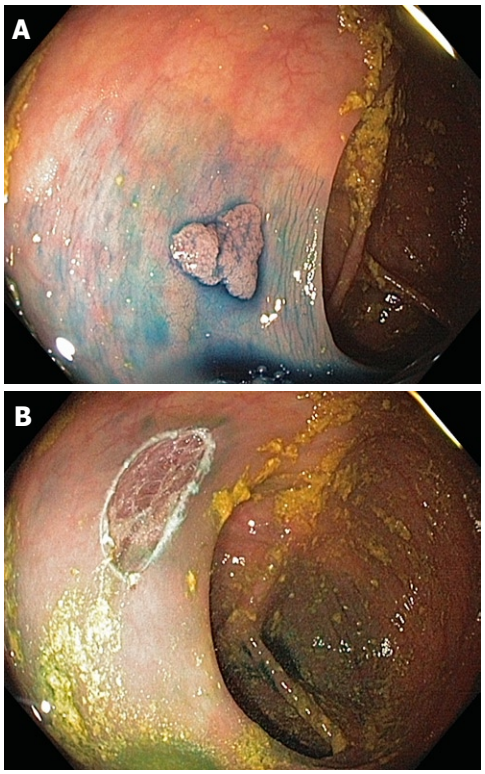

Figure 9 Sessile polyp located in the transverse colon. Demarcation of the polyp margins and surface with standard chromoendoscopy (methylene blue) (A); Endoscopic mucosal resection site (B).

all polyps separately. We recommend sending all polyps separately. The worst-case scenario is to have the pathologist inform the endoscopist of an invasive cancer and not to know whether it was located. We limit the number of polypectomies during one session to no more than 10 and we remove the remaining polyps during following sessions.

Estimation of polyp resectability

This is the result of summarization and feasibility analysis of the above-mentioned steps. Currently, the rules for endoscopic resection have changed. Whereas in the past several criteria clearly mandated surgery (i.e., polyp extending more than 1/3 of the luminal circumference, extending more than two folds location on the ileocecal valve, large, flat villous tumors), currently these criteria are not a contraindication for endoscopic polypectomy anymore. We have entered an era of grey-zones, but with the exception of giant polyps located in the cecum, and the increase skills attained by advanced endoscopists, the majority of colonic polyps can be resected endoscopically (Figures 8-10).

Submucosal cushion (injection-assisted-polypectomy)

Submucosal injection is suggested for the colonoscopic resection of a sessile polyp over 15 mm in diameter[3,4,6,9,27-30] (Figure 1). However, any polyp can be removed using injection-assisted polypectomy (IAP). Indeed, some experts propose its use for all polyps on

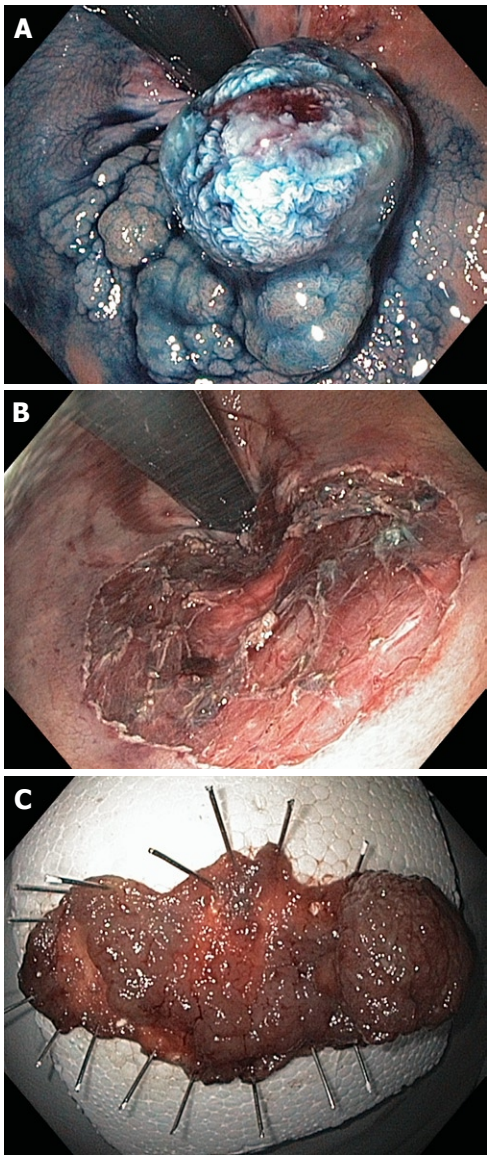

Figure 10 Giant rectal polyp (A), the polyp was resected using endoscopic submucosal dissection-technique (B) and an *en-bloc* resection was possible (C).

two main grounds: (1) achieving a more complete resection; and (2) diminishing the risk of complications such as perforation, bleeding and transmural burn. Thus, it is also reasonable to use IAP for any polyp that is flat, regardless of its size. By raising the polyp from the submucosa a deeper and more complete resection of the neoplastic tissue can be achieved[3,4,6,9,27-30]. In addition, by lifting the submucosa from the deeper layers of the gut wall, the depth of injury is decreased by avoiding the burn at the muscularis propria and serosa[28]. However, submucosal injection even with a large amount of fluid may not avoid perforation if overly large pieces of the polyp are ensnared and resected. Multiple substances are commercially available to perform an IAP. We recommend the use of it for polyps larger than 15 mm. Normal saline is the most popular fluid to IAP. But one can also use a saline-diluted epinephrine mix, saline and dextrose 50% mix, normal saline and methylene blue mixture, sodium hyaluronidate, fibrinogen and hydroxypropyl methylcellulose[3,4,6,27-30]. Some data showing a longer lasting cushioning effect of a normal saline and dextrose mix[29]. We recommend a saline-diluted adrenaline mix (1:10 000) in all parts of the colon, except the cecum, due to the possibility of inducing an ischemic colitis using epinephrine in the cecum. Prophylactic injection of submucosal saline-adrenaline for colon polyps larger than 10 mm is associated with less bleeding and a more complete removal of larger polyps, especially when using the piece-meal resection technique.

TECHNIQUE FOR THE CREATION OF THE PERFECT SUBMUCOSAL CUSHION

The injection needle may be placed into the submucosa at the edge of a polyp. The needle should enter the mucosa almost perpendicularly and penetrate 2-3 mm behind or beside the polyp. While penetrating the needle in the submucosal plane, continuous injection will result in immediate submucosal infiltration of fluid[3,4]. Thus, gentle injection of the fluid by the assistant is recommended, as too much and too rapid injection will create a large bleb and the polyp may not rise to the desired position. The aim is to create a cushion right below the polyp. Therefore, most endoscopists begin with the injection of the substance while the needle is slowly retracted out from its deepest submucosal insertion point. Multiple repeated injections may be required to separate the mucosa and submucosal planes. In addition, if the polyp is large or flat multiple injections may be given around or into the polyp. To accomplish an adequate raise of the proximal side of the polyp, it is important to advance the scope past the lesion, i.e. orally or proximally. Another maneuver is to inject behind the polyp by performing retroflexion. The tip of the needle should only penetrate the mucosa and the upper layer of the submucosa. Thus, the needle should only approach the mucosa at a 30-degree angle and enter the base of the polyp almost tangentially to the surrounding mucosa. Entering the needle in a straight angle results in penetrating the colon wall and injection of the substance in the peritoneal cavity. The amount of in injected material will depend on the size of the polyp. If a polyp fails to elevate (Uno or "non-lifting sign") it may be an indication of infiltration by cancer into the submucosa[31]. In this case it might be wise to mark the polyp side with a tattoo or either clips to aid the surgeon during a subsequent intra-operative localisation or at a follow up colonoscopy. The most commonly used dye for marking is India ink.

ENDOSCOPIC MUCOSAL RESECTION

EMR refers to the removal of parts or all of a mucosal lesion[3,4,6,9,32-34] (Figures 5-8). By definition, any colon polypectomy is a mucosectomy, as the main aim is to remove the entire lesion. For pedunculated polyps the

in-toto resection rates are higher than for sessile or flat ones. However, EMR implies a more aggressive removal method that aims at including enough tissue below and on the surrounding borders the neoplasia (i.e., oncologic resection). The technique of submucosal cushion aims at improving the resection rates when using EMR. Although there are no studies comparing IAP with conventional polypectomy with respect to complication, it is common sense to insist that a "cushion" may result in less bleeding, perforation and possibly transmural burn syndrome. Experimental data demonstrate a benefit in the submucosal cushioning in diminishing deep tissue injury when using APC and various types of electrosurgical currents[28].

EMR USING THE PIECEMEAL-TECHNIQUE ("PIECE-MEAL POLYPECTOMY")

There are no specific size recommendations for piecemeal polypectomy. Piecemeal polypectomy is recommended for sessile or flat polyps larger than 20 mm. When performing piecemeal polypectomy it is recommended to start at the resection at the proximal end of the polyp and to finish distally[3,4,6,9,33,34]. For very large polyps there are no set rules on how many pieces of polyp should be removed during one session. Sessile, flat or laterally spreading polyps 15 mm to 25 mm in diameter can be usually resected in two or three pieces[3,9]. We recommend to never resecting a polyp larger than 15 mm located in the cecum in one piece, unless the submucosal cushion is large enough and the separation of the deeper layers is guaranteed, i.e. the submucosal cushion is so large that it permits ensnaring the "tip of the volcano" containing all adenomatous tissue[3]. The most important aspect of the piece-meal technique is to have the mucosa well raised above the deeper layers using submucosal cushion, i.e., do not be afraid of use repeated injections until all of the polyp has been removed! In order to reduce the depth of tissue injury we recommend performing piecemeal mucosectomy using pure cut current or Endocut.

When resecting polyps with very large heads we like to decrease or shrink (i.e., vasoconstrict) the head of the polyp by injecting adrenaline solution into it. This method is called epinephrine volume reduction (EVR) or Hogan-technique[32]. By using EVR the size of the polyp head decreases making it more amenable to inspection and resection. In addition, the chances of bleeding may be diminished by using EVR[32].

Nonetheless, a complete resection of large polyps is not always possible[3,4,34]. However, application of argon plasma coagulation (APC) to the remaining tissue rests (e.g., tissue rim or small islands of adenomatous tissue) eradication rates of > 90% are achieved and the polyp recurrence is markedly reduced[9,34]. Application of APC can be done immediately after polypectomy or on follow-up[9,34]. Currents used for APC should range between 30 W (cecum) to 60 W (left colon and rectum) with flows ranging from 1-2 L/min[3,9,34]. Patients with sessile adenomas that were removed piecemeal should undergo a surveillance colonoscopy to confirm complete removal 2 mo to 6 mo after initial resection[3,4,9]. Afterwards colonoscopy should be performed every 3 mo to remove any residual neoplastic tissue until a complete endoscopic resection can be documented[9]. Once complete removal has been established, subsequent surveillance needs to be individualized based on the patient's risk factors (e.g., metachronous polyps, family history of CRC) and endoscopist's judgment[3,4,9].

ENDOSCOPIC SUBMUCOSAL DISSECTION

ESD is a novel technique for the resection of superficial neoplastic lesions of the gastrointestinal tract[3,4,5,35] (Figure 10). Theoretically ESD results in a high en bloc (i.e., *in-toto*) resection rates, but requires a high level of skill and long procedure time, sometimes up to four or five hours. The complete resection rates are about 70% to 80% in Europe whereas in Japan these reach 95%[5,35]. The use of these techniques is still limited in the cecum or in the ascending colon, except in the hands of few colonoscopists, especially from Japanese centers[5,35]. However, as ESD is time consuming and involve some risk on account of his technical features, a lesion that is resectable using polypectomy or piece-meal EMR should be treated by these conventional techniques. An absolute indication for ESD could be the need for an en-bloc resection, e.g., those lesions that require precise histological evaluation are depressed lesions and laterally spreading tumors of the non-granular type[5,35]. Other indications for ESD might be lesion with biopsy-induced scares.

The main technical difference of ESD compared to polypectomy or EMR, is the use of a distal attachment cap and the use of different knives and hemostatic devices. As expected, ESD takes also much more time[5,35]. Despite high levels of expertise, colonic ESD results in a relatively higher risk of complications (6%-14%), especially at the beginning of the learning curve and, consequently, demands a thorough knowledge, specific training and expert supervision. Although ESD has the theoretical advantage over piecemeal resection that the entire neoplastic tissue can be removed it still can't be considered a true alternative to EMR in the Western hemisphere. Even in the Japan where colonic ESD has been performed for almost 10 years colonic ESD is still viewed as a clinical research endeavour. Nevertheless, with growing experience and training the results of ESD for selected complex colon polyps are excellent[5,35]. This has been clearly demonstrated in a recent publication by Saito et al who reported on more than 1000 successful colon ESD cases[5]. ESD is an excellent tool to remove large colon polyps in expert hands and thus represents a valuable and accepted method for difficult colon polyps.

Use of clips and endooloops

Any endoscopist performing advanced colon polypec-

tomy should be well trained and versed using clips and loops as these methods are essential to prevent and manage complications[4,12,36]. Endoloops are mainly useful for dealing with polyps with thick stalks[36]. The endoscopist should plan to place the endoloop either before or after the resection as thick pedicles tend to contain large arteries (Figure 2). Endoloops have also been used to close colon perforations[4]. However, this is not a proven standard.

Clips are practical to close mucosal defects, obliterate a stump artery and even close perforations < 10 mm in size[4,12,37] (Figure 2D). Clips are useful to approximate the mucosal edges of a defect. There are two main types of clips: standard and 3-pronged-clip (e.g., TriClip®, Cook Medical, Winston Salem, NC, United States)[38]. Standard clips are either long- or short armed. In addition, a clip which is engineered to enable opening and closing up to five times prior o deployment (Resolution® Clip, Boston Scientific, Nattick, MA, United States) may allow for a better and more accurate repositioning before final deployment. In addition, it may grasp more tissue, resulting in a better approximation of the defect's borders. Although some experts use clips mainly to treat complications such as bleeding and perforation, there is strong data to support its use to prevent post-polypectomy complications such as bleeding[18]. Thus, clips are useful utensils to prevent and treat some complications associated with colon polypectomy. Indeed, we recommend the use of prophylactic clips to seal the polypectomy site in patients who have even minimal abnormalities of the coagulation parameters. When suspecting perforation the use of antibiotics is mandatory[39].

LAPAROSCOPY IN THE MANAGEMENT OF DIFFICULT POLYPS

The advanced colonoscopist should always remember that there exist very efficient surgical and laparoscopic methods that allow removal of large polyps utilizing segmental or wedge resection techniques[40]. Laparoscopy is of special value for large polyps located in the transverse and right colon[40]. Laparoscopic resection is still an alternative to risky ESD or EMR procedures[40]. Conversion to an open laparotomy is only necessary in 3.2 % of the procedures. In some studies lymph node metastasis was found in 14.8% of patients, implying that most of the patients got large lesions or advanced neoplasia[3,4,36]. In addition, there is the possibility of rendezvous methods, combining colonoscopy and laparoscopy: laparoscopy assisted endoscopic resection or LAER), endoscopy-assisted laparoscopic wedge resection (EAWR), endoscopic-assisted laparoscopic translumenal resection (EATR), and endoscopic-assisted laparoscopic segment resection (EASR)[3,40].

COMPLICATIONS OF ADVANCED COLONIC POLYPECTOMY

The two most frequent complications of advanced colonic polypectomy are bleeding and perforation which range from 0.08% to 10%[3,4,9,11,37]. As mentioned above, complications associated with EMR and ESD occur more frequently than after standard polypectomy. Post-polypectomy bleeding can be immediate or delayed. In order to decrease immediate bleeding we often use prophylactic clips, endoloops and injection[36,37]. The second most common complication is perforation[11,37]. Perforation may occur during or after polypectomy or as a result of colon wall stretching while advancing the colonoscope. Perforation can occur immediately after polypectomy if a full thickness piece of colonic wall has removed and later if a necrotic patch of the colon sloughs off as a result of coagulation necrosis ("transmural burn or post-polypectomy coagulation syndrome")[11,37]. The transmural burn syndrome is the most frequent form of "colon perforation". Patients usually present with localized abdominal pain one or more days after polypectomy. In addition, fever may be present. On physical examination the patient has localized tenderness in the area of transmural burn. Most cases of post-polypectomy burn syndrome are "sealed-off" processes which clinically resemble appendicitis or diverticulitis. In essence, the transmural burn results in peritoneal irritation and pain. However, on occasion a sealed perforation may have ensued. In addition, a frank perforation may occur if the necrotic area expands in size and is not sealed off by the patient's omentum. Most patients can be treated with conservative measures, including the use of broad spectrum antibiotics. However, any symptom, sign or laboratory abnormality suggesting an acute abdomen should prompt a surgical approach to repair the defect. The worst clinical scenario is the development of diffuse peritonitis and sepsis.

The most important component to prevent perforation is a good polypectomy technique (see above)[3,4]. Successful treatment of post-polypectomy perforations depends on early diagnosis, immediate use of antibiotics and rapid decision-making[37,39]. If a small perforation is seen during colonoscopy an immediate attempt at closure is warranted[37]. Although surgery has been the standard practice to manage perforations, application of clips and loops has emerged as a useful option to close lesions less than 10 mm, if these are treated as soon as detected[37,39]. In addition, immediate administration of broad-spectrum antibiotics and intravenous fluids and oxygen is mandatory[37,39]. The surgeon should also be immediately notified. The choice of antibiotics should be based on the colon flora, which includes enterobacteria such as *Escherichia coli*, Klebsiella *spp*., *Bacteroides fragilis* and streptococci, such as *Enterococcus faecalis*. Thus, third-generation cephalosporins (e.g., ceftriaxone) or DNA-gyrase inhibitors (e.g., ciprofloxacin) plus an anti-bacteroides agent (i.e., metronidazole) are mandatory[39]. After colonosocopy, the development of unusual abdominal distension or delayed onset of abdominal pain warrants investigation with abdominal examination and radiography or, preferably abdominal CT. In the future novel devices such as the novel OTSC-clip may become attractive options to close larger

defects of the colonic wall[41].

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EDITORIAL

Use of portal pressure studies in the management of variceal haemorrhage

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Abstract

Portal hypertension occurs as a complication of liver cirrhosis and complications such as variceal bleeding lead to significant demands on resources. Endoscopy is the gold standard method for screening cirrhotic patients however universal endoscopic screening may mean a lot of unnecessary procedures as the presence of oesophageal varices is variable hence a large time and cost burden on endoscopy units to carry out both screening and subsequent follow up of variceal bleeds. A less invasive method to identify those at high risk of bleeding would allow earlier prophylactic measures to be applied. Hepatic venous pressure gradient (HVPG) is an acceptable indirect measurement of portal hypertension and predictor of the complications of portal hypertension in adult cirrhotics. Varices develop at a HVPG of 10-12 mmHg with the appearance of other complications with HPVG > 12 mmHg. Variceal bleeding does not occur in pressures under 12 mmHg. HPVG > 20 mmHg measured early after admission is a significant prognostic indicator of failure to control bleeding varices, indeed early transjugular intrahepatic portosystemic shunt (TIPS) in such circumstances reduces mortality significantly. HVPG can be used to identify responders to medical therapy. Patients who do not achieve the suggested reduction targets in HVPG have a high risk of rebleeding despite endoscopic ligation and may not derive significant overall mortality benefit from endoscopic intervention alone, ultimately requiring TIPS or liver transplantation. Early HVPG measurements following a variceal bleed can help to identify those at risk of treatment failure who may benefit from early intervention with TIPS. Therefore, we suggest using HVPG measurement as the investigation of choice in those with confirmed cirrhosis in place of endoscopy for intitial variceal screening and, where indicated, a trial of B-blockade, either intravenously during the initial pressure study with assessment of response or oral therapy with repeat HVPG six weeks later. In those with elevated pressures, primary medical prophylaxis could be commenced with subsequent close monitoring of HVPG thus negating the need for endoscopy at this point. All patients presenting with variceal haemorrhage should undergo HVPG measurement and those with a gradient greater than 20 mmHg should be considered for early TIPS. By introducing portal pressure studies into a management algorithm for variceal bleeding, the number of endoscopies required for further intervention and follow up can be reduced leading to significant savings in terms of cost and demand on resources.

Key words: Variceal haemorrhage; Portal hypertension; Portal pressure; Varices; Hepatic venous pressure gradient

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INTRODUCTION

Portal hypertension occurs as a complication of liver cirrhosis leading to gastro-oesophageal varices, gastrointestinal bleeding, ascites, hepatic encephalopathy and hepatorenal syndrome. These complications are a major cause of morbidity and mortality. The management of these complications of portal hypertension is significant in terms of both resources and time. Moreover with ever increasing pressure on endoscopy services, novel methods of improving and delivering care to such patients should be welcomed. This manuscript concentrates on the potential for portal pressure studies to reduce this burden on endoscopy services.

BACKGROUND TO PORTAL HYPERTENSION AND VARICEAL BLEEDING

Portal hypertension occurs due to a complex interaction between increased resistance in the hepatic microcirculation, increased vascular tone and an imbalance in vasoactive molecules resulting in net vasoconstriction. Increased endogenous vasodilators are produced to compensate with consequent splanchnic arteriolar vasodilation and subsequent increased blood flow in the portal system, further increasing portal pressure[1,2]. Systemic vasodilation and increased cardiac output requiring an expanded blood volume are also associated with these physiological changes.

The resultant portal hypertension leads to the development of varices in about 40% of Childs-Pugh A patients and 60% of those with ascites with an expected incidence of new variceal development of 5% per year[3-5].

CURRENT BURDEN OF PORTAL HYPERTENSION ON ENDOSCOPY SERVICES

Screening

Endoscopy is the gold standard method for screening cirrhotic patients. Current recommendations suggest those with medium to large varices should be treated with B-blockers to prevent bleeding while all others should undergo periodic surveillance endoscopy. Those with compensated cirrhosis and no varices should have endoscopy every 2-3 years while those with small varices should have endoscopy every 1-2 years.

The true incidence and prevalence of cirrhosis in the United Kingdom is unknown. Approximately 4% of the population have abnormal liver tests or liver disease, and 10%-20% of those with one of the three most common liver diseases (non alcoholic fatty liver disease, alcoholic liver disease and chronic hepatitis C) develop cirrhosis over 10-20 years[6]. In a city with a population of 250 000, up to 2000 new cases of cirrhosis could be expected over 10-20 years. Thus the demand on endoscopic screening will continue to increase. Mortality from liver disease has increased from 6 per 100 000 population in 1993 to12.7 per 100 000 population in 2000.

Various non invasive methods of assessing portal hypertension have reviewed by Thabut *et al*[7] Many methods provide an accurate estimation of the presence of severe portal hypertension but not of the presence of moderate portal hypertension in comparison with the Hepatic venous pressure gradient (HVPG). These approaches are aimed at evaluating hyperkinetic syndrome (measuring cardiac index, measurement of splanchnic circulation, baroreflex sensitivity, measurig portal blood flow) or evaluating increased intrahepatic vascular resistance (levels of endogenous vasoconstrictors such as endothelin, markers of hepatic fibrosis eg; procollagen Ⅲ peptide, transient elastography). The only non invasive tools for the detection of oesophageal varices are computed tomographic (CT) scans and oesophageal capsules. Studies have shown CT scanning to be safe and effective and well tolerated with sensitivities ranging from 63% to 93% for the detection of all varices and a sensitivity of 56% to 92% for detection of large varices. When oesophageal assessment for varices by capsule endoscopy is compared to standard endoscopy, it has been shown to have sensitivity of 68% to 100% and specificity of 88% to 100%, with patients significantly preferring capsule endoscopy to standard endoscopy.

CURRENT MANAGEMENT OF PORTAL HYPERTENSION

Pre primary prophylaxis

All cirrhotic patients should be screened at diagnosis. At present there is no indication to use Beta blockers to prevent the formation of varices[8].

Primary prophylaxis

Non-selective beta-blockers are the most commonly used drugs to treat portal hypertension. Propranolol is widely used while nadolol and carvedilol have more recently been shown to have beneficial effects and may be better tolerated in some individuals. Beta-blocker therapy reduces the 2 year bleeding risk from 25% with no treatment to 15% with a reduction in mortality from 27% to 23%. Current consensus does not recommend combination of beta blockers with nitrates in primary prophylaxis[9].

Benefit is seen in treatment of varices greater than 5 mm in diameter[10] With medium to large varices, either non-selective beta-blockers (NSBB) or endoscopic band ligation (EBL) is recommended. Only 30%-40% of patients reduce their portal pressure to greater or equal to 20% from baseline or to under 12 mmHg[11]. The risk of

bleeding returns to that of the untreated population on removal of B blocker with a subsequent higher mortality than the untreated population[12]. Variceal band ligation is as effective as propranolol and superior to isosorbide mononitrate in preventing first variceal bleeds[13].

Secondary prophylaxis

Variceal band ligation combined with a beta-blocker is recommended as secondary prevention for oesophageal variceal haemorrhage. Band ligation is safer and more effective than sclerotherapy in treatment of recurrent bleeding from oesophageal varices[14]. Failure of standard treatment occurs in 10%-15% of acute variceal bleeds.

Transjugular intrahepatic portosystemic shunt (TIPS) can be used to prevent variceal rebleeding and is more effective in preventing rebleeding than endoscopic therapy[15,16]. In a recent study, the early use of TIPS in patients with cirrhosis and variceal bleeding has been assessed- Patients presenting with an acute variceal bleed were treated with vasoactive therapy and endoscopic therapy (band ligation or sclerotherapy) and then randomised to early TIPS with an extended polytetraflouroethylene stent within 24-72 h of presentation or continuation of vasoactive treatment, beta blockers and longterm endoscopic band ligation. It was concluded that patients with acute variceal bleeds with a hepatic venous pressure gradient of 20 mmHg or above are at a high risk of treatment failure and the early use of TIPS in these patients is associated with a significant reduction in treatment failure and mortality[17].

Pharmacological management of acute variceal bleeding

The primary aim is to correct hypovolaemia, resuscitate the patient and obtain haemostasis hence preserving tissue perfusion and maintaining haemodynamic stability. Prolonged hypovolaemia increases the risk of complications such as infection and renal failure which are associated with higher mortality and rebleeding rates[18,19].

Early administration of vasoactive drugs facilitates endoscopy, improves control of bleeding and reduces 5 d rebleeding rates[20-22]. In addition, drug therapy will improve the outcome even if commenced after endoscopic sclerotherapy or band ligation[23,24]. Antibiotics and vasoactive drugs such as glypressin and somatostatin are the only drugs shown to improve survival in an acute variceal bleeding episode and should be continued for five days to prevent early rebleeding.

Conflicting results have been obtained in studies assessing the efficacy of somatostatin and long acting analogues in control of variceal haemorrhage- modest reductions in hepatic blood flow and wedged venous pressure have been reported by some groups, others have found no effect on portal pressure[25,26]. Azygos blood flow as a measure of collateral blood flow has been shown to reduce with somatostatin. In a meta-analysis, somatostatin proved to be effective in controlling variceal haemorrhage, without a beneficial effect on mortality. When compared with sclerotherapy, treatment with somatostatin and octreotide resulted in fewer side effects with equal efficacy. Finally, when combined with endoscopic therapy, somatostatin, octreotide and vapreotide proved to be more effective than placebo[5]. Vasoactive therapy with a single agent is as effective as endoscopic therapy[27-29].

Endoscopic management of acute variceal bleeding

Endoscopic therapy should be performed within 12 h of admission. A meta-analysis of seven placebo-controlled trials showed that variceal band ligation therapy was superior to sclerotherapy in terms of rebleeding (all-cause mortality and death due to bleeding in patients with bleeding oesophageal varices)[30]. In the case of uncontrollable haemorrhage, balloon tamponade may be necessary as a bridge to more definitive treatment but should ideally be used for no more than 24 h. When TIPS or other shunts are not possible, novel therapeutic options include tissue glue (even in oesophageal varices) and in future, self expanding oesophageal metal stents may have a role in refractory oesophageal variceal bleeding[31].

Endoscopic follow-up after variceal bleeding

Recurrent variceal bleeding can be as high as 50% within the first 24 h and 80% within one year[32]. Patients with cirrhosis who have had a bleed should receive a combination of beta blockers and band ligation as it results in lower rebleeding compared to either therapy alone[7].

A meta-analysis of 895 patients in 12 trials comparing propranolol with placebo in the secondary prevention of variceal haemorrhage found propranolol monotherapy more effective than placebo in reducing risk of death and rebleeding however, only 30%-40% of patients reduce their portal pressure to greater or equal to 20% from baseline or to under 12 mmHg[10] and the risk of bleeding returns to that of the untreated population on removal of B blocker with a subsequent higher mortality than the untreated population[11]. TIPS should be considered to prevent rebleeding when combination pharmacological and band ligation therapy are not available, cannot be tolerated or fail.

In a recent meta-analysis by Li *et al*[33], controlled trials evaluated the efficacy of EBL *vs* pharmacological therapy for the primary and secondary prophylaxis of variceal hemorrhage in patients with cirrhosis. Six hundred and eighty seven patients from six trials were reviewed comparing EBL with beta-blockers plus isosorbide mononitrate for secondary prevention. There was no effect on either gastrointestinal bleeding [RR 0.95 (95% CI: 0.65 to 1.40)] or variceal bleeding [RR 0.89 (95% CI: 0.53 to 1.49)]. The risk for all-cause deaths in the EBL group was significantly higher than in the medical group [RR 1.25 (95% CI: 1.01 to 1.55)]; however, the rate of bleeding related deaths was unaffected [RR 1.16 (95% CI: 0.68 to 1.97)] and it was concluded that beta-blockers plus isosorbide mononitrate may be the best choice for the prevention of rebleeding

Lo *et al*[34] comment on the long-term effectiveness

and survival of endoscopic variceal ligation (EVL) with nadolol and ISMN in the prevention of rebleeding from esophageal varices. The study demonstrated that EVL was definitely better than combination drug therapy in terms of prevention of rebleeding from oesophageal varices. Blood requirements were slightly lower in the patients who underwent repeated EVL than in those who received nadolol plus isosorbide-5-mononitrate (ISMN). On the other hand, the survival in patients treated with combination drug therapy appeared to be better than in those treated with repeated EVL. Nonetheless, b-blockers had to be discontinued in up to 25% of patients because of adverse effects. EVL is the preferred approach among those patients in whom b-blockers fail or are intolerable

Following successful haemostasis in an acute variceal bleed, Silvano *et al*[35] reported the mean number of endoscopy sessions required for variceal obliteration following an acute variceal bleed was 2.8 with a range of 1-7.

HEPATIC VENOUS PRESSURE GRADIENT MEASUREMENT

Background

Portal pressure, in chronic liver diseases, is commonly measured by the HVPG, defined as the difference between wedged (occluded) and free hepatic venous pressures with normal values ranging between 1 mmHg and 5 mmHg. It is an acceptable indirect measurement of portal hypertension, because wedged hepatic venous pressure is very close to portal venous pressure in most chronic liver diseases, particularly in alcoholic and viral (B and C) cirrhosis[36-39]. It thus acts as a marker of transmural variceal pressure. HVPG is reproducible and the best predictor of the complications of portal hypertension in adult cirrhotics. Varices develop at a HVPG of 10-12 mmHg with the appearance of other complications with HPVG > 12. Variceal bleeding does not occur in pressures under 12 mmHg[40-43]. HPVG > 20 mmHg measured early after admission is a significant prognostic indicator of failure to control bleeding varices, indeed early TIPS in such circumstances reduces mortality[44].

The procedure is performed under local anaesthetic *via* the internal jugular vein using a balloon catheter. Techniques have been improved since HVPG measurement was first proposed substituting the use of a straight catheter with a balloon catheter positioned into a large hepatic vein which can be inflated to block blood flow and deflated allowing measurement over a larger liver volume making measurement easier, quicker to perform and repeatable across different liver areas and between different examiners.

It is a safe procedure with Bosch *et al*[45] reporting no complications in over 10 000 procedures. Thabut *et al*[7] reported minor complications in < 1% of 13 000 procedures, mainly transient cardiac events. Midazolam can be used for conscious sedation and will not alter hepatic pressures. At present, the HVPG is not part of the routine investigation in chronic liver disease and is not incorporated in prognostic scores.

Use of HVPG

At present, the main indications of HVPG measurement in adults are the diagnosis of portal hypertension, the assessment of the effects of drug therapy, the preoperative evaluation for liver resection surgery in patients with cirrhosis and hepatocellular carcinoma, the quantification of disease progression/regression of chronic liver disease due to infection with hepatitis C or B virus and identification of the need for TIPS revision[46].

Using HVPG to achieve therapeutic targets

Changes in portal venous pressure induced by drugs are similarly reflected in wedged hepatic venous pressure, and therefore the HVPG is an adequate measure of drug effects on portal pressure. The risk of primary bleeding and rebleeding is much lower in cirrhotic patients with a good response to treatment[43,47-49] and baseline and repeat measurements of HVPG have been recommended for the management of patients with cirrhosis in the setting of pharmacologic prophylaxis of variceal bleeding.

A reduction in HVPG of more than 20% from baseline or a final HVPG less than 12 mmHg, results in a reduction of the complications of cirrhosis, improved survival and reduction in variceal size.51[10,50-52]. Reaching these targets may also lead to improvement in the development or accumulation of ascites, sbp, hepatorenal syndrome and subsequent death[53,54]. This target is achieved in only approximately 30% of patients. Even reduction of more than 10% from baseline reduces the risk of first variceal bleeding. HVPG response to intravenous propranolol may also be used to identify responders to beta blockers however further studies are required[7].

Current pharmacological therapy used in the treatment of portal hypertension only addresses the increased portal blood flow component of the syndrome. The intrahepatic resistance component has yet to be widely explored with new drugs. For this purpose, repeated HVPG measurements may be necessary until less invasive methods of evaluating portal pressure become available.

HVPG monitoring in primary prophylaxis

HVPG is not routinely used in the pre-primary prophylaxis other than in the context of clinical trials.

In primary prevention, only 30%-40% of patients with non selective beta blockade or endoscopic band ligation for primary prophylaxis will lower their portal pressure by more than or equal to 20% from their baseline or < 12 mmHg and it is well accepted that in these cases, there is an increased risk of bleeding-Merkel *et al*[47] reported that the cumulative probability of primary variceal bleeding was significantly higher among hemodynamic non responders to B-blockers. Furthermore, Groszmann *et al*[43] reported none of the patients who achieved an HVPG of ⩽ 12 mmHg during subsequent

measurements experienced a hemorrhage.

HVPG measurement could be used as the investigation of choice in those those patients who have confirmed cirrhosis in place of endoscopy for intitial variceal screening. In those with elevated pressures, primary medical prophylaxis could be commenced with subsequent close monitoring of HVPG thus negating the need for endoscopy at this point.

HVPG monitoring in secondary prophylaxis

Early HVPG measurement has been identified as an independant predictor of short term prognosis in patients with acute variceal bleeding treated with standard endoscopic and pharmacological management and patients not achieving the suggested reduction targets in HVPG have a high risk of rebleeding despite endoscopic ligation. These patients may not derive significant overall mortality benefit from endoscopic interevention alone and may require TIPS or liver transplantation[49]. In the setting of an acute bleed, HVPG greater than 20 mmHg at endoscopy is one of the variables most consistently found to predict 5 d treatment failure. 10%-15% of patients in the setting of an acute variceal bleed will require repeat endoscopic therapy.

TIPS can be used to prevent variceal rebleeding and is more effective in preventing rebleeding than endoscopic therapy[16]. Early HVPG measurements following a variceal bleed can help to identify those at risk of treatment failure who may benefit from early intervention with TIPS.

Garcia-Pagan *et al*[17] have shown that in patients with cirrhosis, in the setting of an acute variceal bleed, and at high risk of treatment failure with a HVPG of $\geqslant$ 20 mmhg, the early use of TIPS is associated with a significant reduction in treatment failure and mortaility This in return, reduces the number of endoscopies being performed in an effort to achieve subsequent haemostasis in the event of a rebleed.

HPVG monitoring is also useful to adapt medical therapy according to response. Such as the addition of ISMN to b-blockers which enhances the fall in portal pressure achieved using only b-blockers and this combined therapy has shown efficacy in preventing variceal rebleeding. Responders to b-blockers have no further decrease in HVPG with the addition of vasodilators and the beneficial effects are restricted to nonresponders[55,56].

Villaneuva *et al*[55] carried out a study on cirrhotic patients following a variceal bleed to assess the value of HVPG-guided therapy using nadolol + prazosin in nonresponders to nadolol + ISMN compared with a control group treated with nadolol + ligation. A Baseline haemodynamic study was performed and repeated within 1 mo. In the guided-therapy group, nonresponders to nadolol + ISMN received nado- lol and carefully titrated prazosin and had a third haemodynamic study. Nadolol + prazosin decreased HVPG in non responders to nadolol + ISMN ($P < 0.001$). 74% of patients were responders in the guided-therapy group *vs* 32% in the nadolol + ligation group ($P < 0.01$). The probability of rebleeding was lower in responders than in nonresponders in the guided therapy group ($P < 0.01$), but not in the nadolol + ligation group ($P = 0.41$). In all, 57% of nonresponders rebled in the guided-therapy group and 20% in the nadolol + ligation group ($P = 0.05$). This study suggests the use of ligation to rescue non responders who have had their medical therapy optimized by close HVPG monitoring.

Therefore, we recommend all patients presenting with variceal haemorrhage should undergo HVPG measurement and those with a gradient greater than 20 mmHg should be considered for early TIPS. The remainder should have a trial of B-blockade, either intravenously during the initial pressure study with assessment of response or oral therapy with repeat HVPG six weeks later. As nonresponders to drugs tend to rebleed early, many patients rebleed before their hemodynamic response is evaluated. Early hemodynamic measurements are recommended.

A potential algorthym for the use of portal pressure measurement in management of variceal bleeds is described in Figure 1.

Prognostic value of HVPG

This remains under debate. HVPG response correlates with morbidity and mortality from portal hypertension. Some authors have proposed that HVPG measured after bleeding[57,58] or sequential HVPG recordings may predict survival, whereas others have not found any predictive value of HVPG for survival[59,60]. As the level of portal hypertension has been correlated with both histologic damage and degree of liver failure[61] it could be proposed that HVPG be used as a prognostic indicator along with Child Pugh, Meld and UKELD Scores[62]. Increasing HVPG has also been associated with increased annual risk of hepatocellular carcinoma development.

Limitations of HVPG

Although HVPG measurement is safe and relatively simple, it is invasive and some difficulties still exist in relation to its use as a screening tool. HVPG calculation must be standardized. The hemodynamic data available is difficult to interpret with variation seen in treatment used, percentage of patients with alcoholic liver disease, time of follow-up, percentage of patients in Child's class C, and in the interval of time after which the second HVPG measurement was performed[10,63-65]. A significant relationship was found between a longer time interval between two HVPG measurements and a lower benefit from HVPG reduction[66]. Furthermore, HVPG is likely to decrease with alcohol abstinence and this will affect results of such studies. Further clinical trials are required to evaluate prospectively the prognostic value of HVPG changes for the risk of bleeding and to assess HVPG guided therapy. Trials assessing pharmacological management in primary prophylaxis should include HVPG measurements.

HVPG measurement is expensive with an estimated

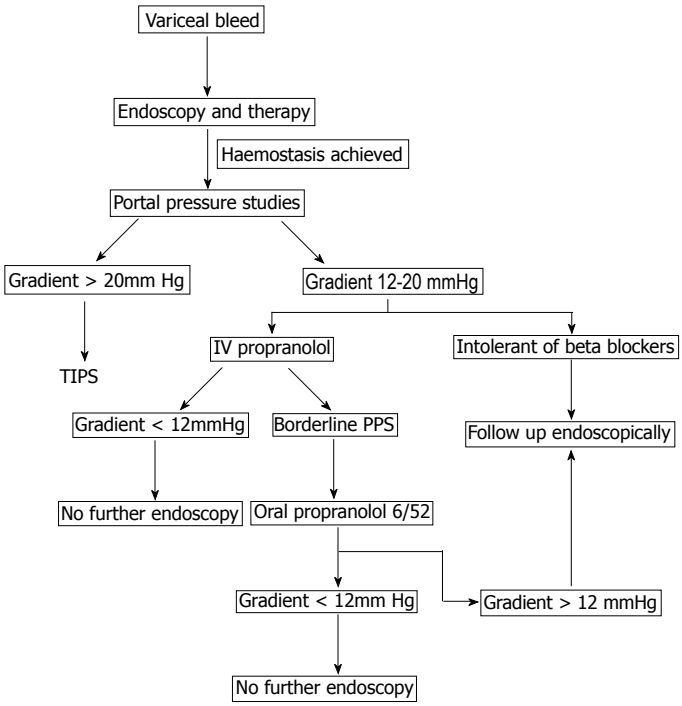

Figure 1 Algorithm for the use of portal pressure studies in the management of portal hypertension. TIPS: Transjugular intrahepatic portosystemic shunt.

cost of US $4000 per procedure due to the cost of equipment (radiology apparatus, pressure recorder and monitors), one use only products (venous introducer, catheter to reach hepatic vein, guide wire, balloon catheter, disposable pressure transducer and contrast), personnel to carry out the procedure and required observation period in hospital following the procedure[46].

CONCLUSION

As the prevalence of cirrhosis continues to rise in the western world, portal hypertension plays a crucial role in the transition from the preclinical to the clinical phase of cirrhosis with the subsequent complications being both a major cause of death and liver transplantation. It also places a large burden on the health service in terms of resources required to deal with the complications of cirrhosis. The ideal scenario is that portal hypertension is detected early in a cost effective manner prior to complications developing.

Universal endoscopic screening of cirrhotics for varices may mean a lot of unnecessary procedures as the presence of oesophageal varices is variable with prevalence ranging from 24%-80% and this puts a large time and cost burden on endoscopy units to carry out both screening and subsequent follow up of variceal bleeds[67]. Up to 50% may not have developed varices 10 years after the diagnosis of cirrhosis. Studies have shown a lack of agreement between endoscopists in grading the size of varices[68-70] with endoscopic experience being one of the variables.

Endoscopy may be uncomfortable, invasive, costly and time consuming and patient preference is obviously paramount relating to compliance and hence to the success of a screening programme which in turn has an impact on the services required and overall cost effectiveness. As the majority of patients are asymptomatic and require a procedure that they may judge as unpleasant, may require sedation and has associated complications, compliance can be low and this is a major factor in the effectiveness of screening programmes. It is therefore essential that studies in this area are ongoing to identify possible alternatives to endoscopy as a screening tool for oesophageal varices.

A less invasive method to identify portal hypertension and hence those requiring endoscopy would prove beneficial both in reducing the number of screening endoscopies performed and also identifying those at high risk of bleeding therefore allowing earlier prophylactic measures to be applied with the aim to reduce subsequent acute bleeding presentations. Various methods have been studied but no alternative for endoscopy has yet been found.

Not all those who initially respond to medical therapy remain good responders and data beyond one year follow up is lacking hence longer term studies are essential as worsening HVPG despite beta blocker treatment is a significant predictor of death independent of Child Pugh/MELD scores[46]. Villanueva *et al*[71] who report follow up at 24 mo of cirrhotic patients with oesophageal varices undergoing HVPG monitoring whilst undergoing primary prevention with initial IV propranolol and subsequent treatment with nadolol suggest an HVPG reduction of ⩾ 10% from baseline should be the target and that the acute reponse to beta blocker can be used to predict the long term risk of first bleeding wth acute

responders having a significantly lower risk of both first variceal bleeding and development of ascites however further longterm studies are required.

In a debate regarding the use of HVPG monitoring as a guide for prophylaxis and therapy of bleeding and rebleeding, Thalheimer *et al*[72] state that relying on haemodynamic response status cannot be recommended in current clinical practices due to discrepancies in the studies to date as a result of variation in treatment combinations, aetiology of liver disease, Childs Pugh scoring of patients, variation in timing of follow up and inaccurate recording of responder status or repeat HVPG measurements. This clearly indicates the need for ongoing research in this area. The number of patients required to carry out a randomized control trial comparing beta blocker therapy and HVPG monitoring with unselected beta blocker treatment are large (n = 600) and have financial and resource implications for a study group to take on[73].

Raines *et al*[74] proposed a model to evaluate the cost and efficacy of routine HVPG measurement to guide secondary prophylaxis of recurrent variceal bleeding-whilst combination therapy (beta blockers and band ligation) with two HVPG measurements was expensive, it became cost-effective at 1 year compared with standard prophylaxis with combination pharmacotherapy. The cost-effectiveness of haemodynamic monitoring to guide secondary prohylaxis of recurrent variceal bleeding is highly dependent on local hepatic venous pressure gradient measurement costs, life expectancy and rebleeding rates.

We propose that by introducing portal pressure studies into a management algorithm for variceal bleeding, the number of endoscopies required for further intervention and follow up can be reduced leading to significant savings in terms of cost and demand on resources. Further studies are required to assess the cost effectiveness of HVPG measurements in the management of variceal bleeding.

With the development of further pharmacological interventions in the management of variceal bleeding, portal pressure studies are likely to become increasingly important in assessing the risk of bleeding and prognosis and this is an area that requires further study.

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EDITORIAL

Stenosis in gastric bypass: Endoscopic management

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Abstract

Gastric bypass is a treatment option for morbid obesity. Stenosis of the gastrojejunal anastomosis is a recognized complication. The pathophysiological mechanisms involved in the formation of stenosis are not well known. Gastrojejunal strictures can be classified based on time of onset, mechanism of formation, and endoscopic aspect. Diagnosis is usually obtained by endoscopy. The two main treatment alternatives for stomal stricture are: endoscopic dilatation (balloon or bouginage) and surgical revision (open or laparoscopic). Both techniques of dilation [through-the-scope (TTS) balloon dilators, Bougienage dilators] are considered safe, effective, and do not require hospitalization. The optimal technique for dilation of stomal strictures remains to be determined, but many authors prefer the use of TTS balloon catheters. Most patients can be successfully treated with 1 or 2 sessions. The need for reconstructive surgery of a stomal stricture is extremely rare.

Key words: Gastric bypass; Gastrojejunal anastomosis; Balloon dilation; Stricture; Endoscopic dilation; Bougienage dilation; Stenosis of the anastomosis; Obesity

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INTRODUCTION

Obesity has become one of the main health problems in industrialized countries. This XXI century pandemic has important consequences: an increased risk of suffering from cardiovascular disease, diabetes, hypertension, dyslipidemia, gastroesophageal reflux disease, certain cancers, as well as an increased mortality[1]. Roux-en-Y gastric bypass (RYGBP) is currently one of the most common surgical procedures for the treatment of morbid obesity [defined as a body mass index (BMI) ⩾ 40 kg/m^2)[2-7]. The success of this procedure´s restrictive component requires the construction of a small gastric pouch and a small gastrojejunostomy (GJ). Over the past years, laparoscopic bypass has undergone great development. This route offers clear advantages compared to open surgery, such as: less blood loss during surgery, less postoperative pain, a lower incidence of wound infections, a shorter hospital stay and a shorter period of recovery[1]. Stenosis of the GJ occurs in approximately 3%-27% after gastric bypass, and must be suspected when the patient experiences dysphagia (initially with solids and subsequently with liquids), nausea and vomiting[1-22]. The methods for treating anastomotic stricture range from surgery to various forms of endoscopic therapy. Endoscopic dilation (ED) by means of a balloon or bougie is considered the treatment of choice[1,4,6,8,9,11-20,22-30]. ED is safe, effective and reduces the need for revision surgery[11].

ETIOLOGY

The etiology of this complication is mulifactorial. The

pathophysiological mechanisms involved in the formation of stenosis are not well known, although situations such as stomal ulcer, reflux, ischemia of the suture, retraction of the scar, or an inadequate technique, may contribute to its appearance[2,9]. Several technical features associated with the surgical procedure have been considered risk factors for the development of gastrojejunostomy strictures. These include the size of circular staple anastomoses[12,31], the retrocolic or antecolic positioning of the Roux limb, or the initial size of the anastomosis[21]. The method of constructing the gastrojejunal anastomosis seems to have an impact, as it seems that circular staples are more implicated than either linear staples or a completely hand-sewn anastomosis[8,29,32,33]. The route of the Roux limb (antecolic *vs* retrocolic) does not appear to affect the rate of this complication[32,33]. Nguyen showed that this complication is more common after laparoscopyc RYGBP than after open RYGBP[10]. It has been proposed that the precarious blood supply to the pouch or the development of a subclinical leak at the level of the gatrojejunostomy are the reasons that best explain the formation of stricture after laparoscopic RYGBP[8,30]. Intraoperative endoscopy or the infusion of methylene blue into the gastric pouch *via* a nasogastric tube to assess the integrity of the gastrojejunal anastomosis, reduces the likelihood of postoperative leaks, which complicate approximately 1.4% to 2% of RYGBP[11]. Gastro-gastric fistula can result in recurrent anastomotic strictures due to the large amount of acid that flows from the gastric remnant into the pouch, which results in marginal ulceration followed by stenosis[34,35]. An important factor that should be taken into consideration when analyzing the etiology of this complication is the anatomy and mechanism of RYGBP as a weight-loss procedure (it causes gastric restriction and prevents dumping syndrome). To date, there has been no consensus on the ideal size of the gastrojejunal anastomosis. Most surgeons will agree that 15 mm is a reasonable diameter that will prevent the formation of early strictures as well as dumping syndrome, while creating restriction[15].

CLASSIFICATION

Gastrojejunal strictures can be classified based on time of onset (acute or late), mechanism of formation (membranous, cicatricial, granulomatous), and endoscopic aspect (grade 1 to 4)[7,15,21].

Time of onset

Acute strictures are rare and appear in the immediate postoperative period. The reason behind acute strictures is a technical error in judgment. Late strictures are the most common form and are seen, on average, 52 d postoperatively, when patients transition from soft to solid food[8,12,29].

Mechanism of formation

Membranous strictures occur after a period of prolonged fasting. These are easily treated by endoscopic balloon dilatation; cicatricial strictures are a direct consequence of erosion by a foreign body, ulceration, and anastomotic leaks. These are characterized by intense fibrosis and respond unpredictably to endoscopic balloon dilation. Surgical revision is not uncommon. The pathogenesis of granular strictures is not completely understood. It has been suggested that granular strictures occur from either a lack of mucosa-to-mucosa apposition (edges separated by two thicknesses of bowel wall), which would cause the raw edges to heal by secondary intention, or from tissue necrosis beyond the staple line with subsequent inflammation, delayed epithelization, and fibrosis. This type of stenosis was seen in anastomoses with ischemia due to tension[12,15,21].

Endoscopic aspect

Post-gastric bypass gastrojejunostomy strictures can be graded endoscopically and classified into four groups[7]: grade Ⅰ: Mild stenosis, which will allow a 10.5-mm endoscope to pass; grade Ⅱ: Moderate stenosis, which will accommodate an 8.5 mm pediatric endoscope; grade Ⅲ: Severe stenosis, through which a guide-wire can be passed; grade Ⅳ: Complete/near-complete obstruction, which is nontraversable.

DIAGNOSIS

In order to arrive to a correct diagnosis, it is crucial to have a clinical suspicion of anastomotic stricture. Strictures can be suspected by symptoms of dysphagia, nausea, vomiting, and abdominal pain. Diagnosis is usually obtained by endoscopy, which also allows to rule out other causes of pain, nausea or vomiting. It can also be diagnosed by radiological studies with Gastrografin, especially if leakage is suspected[1,7,11,15,29].

Time to stricture

The mean time to diagnosis of GJ stenosis from surgery to the initial endoscopy is variable. However, most patients with anastomotic strictures were diagnosed within 3 mo from the surgery[1,6-9,12-14,17,19,21-23,28-30].

Criteria for diagnosing stenosis of the gastrojejunal anastomosis

Stomal stricture is usually defined by a resistance or inability to pass a standard gastroscope through the gastrojejunal anastomosis, suggesting a luminal size of < 10 mm. The outer diameter of the endoscope used in different studies ranges between 8.5 mm and 9.6 mm[1,5,6,8,9,12,14,17,19,28-30].

TREATMENT OPTIONS

The two main treatment alternatives for stomal stricture are: endoscopic dilatation and surgical revision (open or laparoscopic).

Dilatation

TTS balloon dilators: There are several options for

dilating a stenotic gastrojejunal anastomosis. The optimal technique for dilation of stomal strictures is yet to be determined; however many authors prefer the use of through-the-scope (TTS) balloon catheters and dilating them to at least 15 mm in the first session to decrease the chance of recurrence[11]. After having followed this protocol, most patients require only one or two dilatations[1,5,6,8,9,12,17-19,21,22,28,29]. TTS balloon dilators provide radial dilation and gradual expansion, thus preventing excessive pain and minimizing the likelihood of perforation. The balloons may be inflated with water, saline solution, or water-soluble contrast medium. The inflation device, which attaches to the balloon catheter hub, contains a pressure gauge in order to ensure proper balloon inflation. Fluoroscopy is not required for positioning the balloon, but should be used liberally in difficult cases[22]. The patient is positioned in the left lateral position and conscious sedation is applied. The anastomotic stricture is visualized, and the deflated balloon is inserted through the working channel of the endoscope and past the stricture under direct visualization. The deflated balloon should be positioned so that the anastomotic stricture is aligned with the balloon's midpoint. Given that the optimal diameter of the gastric outlet is of about 12 mm, the 12-15 mm balloon is ideal. While monitoring for signs of patient discomfort, the balloon is gradually inflated. The position and inflation of the balloon are monitored by direct endoscopic visualization. The position of the balloon is maintained for 1 min after complete inflation to ensure adequate dilatation of the stricture. Once the dilatation is complete, the patient is discharged home and dietary instructions are given.

Bougienage dilators: The efficacy of Bougie dilatations (Savary-Gilliard, Eder-Puestow) in the treatment of stomal strictures after bariatric surgery is very limited[7,14,20,27,30]. Dilation with Savary-Gilliard bougies is a popular method for treating esophageal strictures. Savary-Gilliard dilators (Wilson-Cook Medical Inc, Winston-Salem, NC) are tapered dilators made of polyvinyl chloride. They are relatively rigid and possess a hollow central channel, which allows for insertion over a guidewire. Savary dilators are available in 1 mm (or 3-French) increments from 5 mm in diameter to 20 mm (15 to 60 French). The procedure is usually performed in an outpatient endoscopy-suite, using a combination of narcotic analgesic and sedative hypnotic agents to produce conscious sedation. The patient is placed in the left lateral decubitus position on a fluoroscopy-table. A diagnostic upper endoscopy is performed, and the approximate size of anastomotic stricture is determined. A Savary guide-wire is inserted through the working channel of the endoscope and passed through the stricture under endoscopic visualization. The position of the guide wire is usually confirmed by fluoroscopy. The endoscope is removed while an assistant holds the wire in place. Serial fluoroscopic spot images are taken to verify that the guide wire does not migrate during the removal of the endoscope or during the transfer of the dilators. The initial size of the dilator should be slightly smaller than the diameter of the stricture. An assistant is necessary to control the long guide wire and transfer dilators to the endoscopist during the procedure. Insertion and removal of the first dilator should be visualized fluoroscopically. Incrementally larger dilators are passed serially until moderate resistance is met. Once resistance is encountered, no more than three consecutive dilators should be passed ("rule of threes"). Additionally, the procedure should be terminated soon after traces of blood are visualized on the tip of the dilator. Dilatation to at least 12 mm (36 French) is optimal. A repeat endoscopy is advised so as to visualize the newly dilated segment and to exclude the presence of active bleeding. The patient is then allowed to recover from conscious sedation and discharged home on a clear liquid diet. Once tolerated, a soft diet is recommended for 24 h to 48 h after the procedure, after which the standard post-gastric bypass diet is encouraged.

Radioscopic monitoring

An important aspect to consider is when the fluoroscopic monitoring during dilation is needed. Published studies are not clear when it comes to describing this aspect. The minority of them clearly manifest not using fluoroscopy during dilation[5,8,22,27,29], others claim to have used it in all or in one of their patients[9,10,12,14,18,24,25,28], and finally, others do not make any sort of comment in this regard in their publications[1,4,6,7,13,17,19,21,30]. Our experience demonstrates that carrying out dilations in patients with stenosis of the gastric bypass anastomosis is possible without fluoroscopic guidance, allowing to carry out the technique in the simplest manner, in the same endoscopy room, without radiation for the patient or for the medical staff, and probably for a shorter duration[22].

Advantages and disadvantages of endoscopic treatment

Both techniques (TTS balloon dilators, Bougienage dilators) are safe and do not require hospitalization. Advantages of balloon dilatation include the fact that fluoroscopy is often not required and the stricture is dilated under direct endoscopic visualization. Balloon dilation also takes less time than guide-wire techniques. Additionally, balloon dilation allows the ability to dilate the stoma while performing the diagnostic endoscopy[27]. Savary dilatation requires multiple bougie passages to dilate a strictured segment, which may contribute to an increased awareness and pain during the procedure. Even so, it is important to be familiar with both techniques, because balloon dilatation may not be technically possible in patients with very tight strictures[28]. The possibility of reusing the Savary-Gilliard dilator also allows for a lower cost than that of balloon dilation[14,30].

Endoscopic alternatives

Endoscopic diathermia incision has also been used as anecdotal treatment of stomal stenosis[1,23,36,37]. The en-

Table 1 Dilation treatment of gastrojejunal strictures after gastric bypass-clinical data of reported series

Author	*n*	Stricture rate (%)	Time to stricture	Dilation method	Strategy	No. of Sessions	Success rate (%)	Complications	Follow-up
Rossi[18]	38	17	NR	TTS balloon	Stoma no larger than 15 mm	1: 47.3% 2: 47.3% 3: 5.2%	100	No	12 m
Goitein[7]	19	5.1	45 d	TTS balloon Savary (10/19)	Initial: 8-18 mm	1: 22% 2: 39% ⩾ 3: 35%	100	1 microperforation 1.60%	21 m
Barba[12]	24	11	< 3 mo	TTS balloon	Mínimum: 15 mm	1: 67% 2: 30% 3: 3%	100	No	> 6 m
Ahmad[8]	14	3.1	2.7 mo	TTS balloon	Mínimum: 15 mm	1: 64% 2: 29% 3: 7%	100	No	18 m
Escalona[30]	53	6.9	51 d	Savary	Up to 11 mm	1: 75.5% 2: 16.9% 3: 5.7% 4: 1.9%	100	1 microperforation 1.90%	NR
Go[29]	38	6.8	7.7 wk	TTS balloon	Initial: 12-15 mm	1-2: 71% ⩾ 3: 29%	95	1 pneumotorax + pneumomediastinum (3%)	1 m
Peifer[9]	43	5.4	50 d	TTS balloon	Up to 15 mm	1: 79% 2: 13.9% ⩾ 3: 6.9%	93	No	1 y
Lee[1]	40	3.7	1855 d	TTS balloon	Stoma > 11 mm < 15-18 mm	1: 42.5% 2: 17.5% 3: 27.5% >3: 12.5%	100	No	6 m
Kretzschmar[23]	13	3	2.5 mo	Fogarty Grüntzig balloon	Stoma ⩾ 12	1: 86.3%	77	No	3.7 y
Bell[28]	3	11	10 wk	TTS balloon Savary	Stoma ⩾ 12	1: 33.3% ⩾ 2: 66.6%	100	No	12 m
F-Esparrach[14]	24	6	69 d	Savary	Final diameter: 12.8 mm	1: 45.8% 2: 50% 3: 4.1%	100	No	343 d
Matthews[21]	13	27	< 3 mo	TTS balloon	NR	1: 53.8% 2-4: 46.1%	100	No	12 m
Da Costa[19]	105	7.8	3 mo	TTS balloon	NR	1: 57.1% 2: 27.6% ⩾ 3: 15.2%	100	Perforation 1.8%	NR
Campillo[13]	5	8.1	< 3 mo	TTS balloon	Maximum:15 mm	1: 60% 2: 40%	100	No	24 m
Ukleja[17]	61	6	2 mo	TTS balloon	Ranged from 6 to 18 mm	1: 28% 2: 33% 3: 26% > 3: 13.1%	100	Perforation 2.2%	NR
Alasfar[5]	29	23	Median: 52 d	TTS balloon	12 mm	1: 86% 2: 3.5% 3: 10.5%	100	No	NR
Mathew[6]	58	6.5	66.2 d	TTS balloon	Stoma no larger tan 12 mm	1: 40% 2: 31% 3: 16% > 3: 10%	97	Perforation 3.2%	NR
Espinel[22]	22	4.1	126 d	TTS balloon	Initial: 12-15 mm	1: 68.1% 2: 27.2% ⩾ 3: 4.5%	100	1 microperforation (4.5%)	27 m

NR: Not reported; TTS: Through-the-scope.

doscopic incision was performed by placing the papillotome deep within the stoma and directing the cutting wire against the staple line. An alternate cutting and coagulating current was applied in repeated, short (1-3 s)

bursts until the desired diameter was reached. However, cannulation of the narrowed stoma with the papillotome can be difficult and hazardous in the hands of inexperienced endoscopists.

Surgical revision

The need for reconstructive surgery of a stomal stricture is extremely rare (0.4%)[15]. This terapeutic option is generally used when no improvement is achieved after four consecutive endoscopic dilations. In most cases surgical revisions are performed laparoscopically. Laparoscopic revision of a strictured anastomosis is a technically challenging procedure that is expensive and carries a significant morbidity.

GOAL OF THE TREATMENT

The endpoint for gastrojejunal anastomotic stricture dilatation is yet to be established. While the immediate goal is to provide symptomatic relief, a narrow stomal outlet must be maintained so that long-term weight loss is achieved. In a 1996 survey of the American Society for Bariatric Surgery, members generally agreed on a gastrojejunal anastomotic diameter of 12 mm[38]. For Lee *et al*[1] the goal of dilation was to obtain a stoma > 11 mm in diameter, but not excessively large (they do not recommend to dilate the stoma above 15-18 mm), in order to maintain the restrictive integrity of the bypass surgery to ensure continued weight loss and to minimize the risk of major complications. Barba *et al*[12] dilate to get at least a size of 15 mm in order to reduce the possibility of symptomatic recurrence.

RESULTS

The results of the various series are shown in Table 1. Stenosis of the GJ occurs in approximately 3%-27% after gastric bypass. Most patients with anastomotic strictures were diagnosed within 3 mo of surgery. ED by means of a balloon or bougie is considered the treatment of choice. Both techniques (TTS balloon dilators, Bougienage dilators) are safe and do not require hospitalization. The optimal technique for dilation of stomal strictures remains to be determined, but many authors prefer the use of TTS balloon catheters. The dilation strategy is variable among different authors, although the goal of treatment is similar: dilating them to at least 15 mm to decrease the chance of recurrence. The success rate ranges from 77%-100%, and in the majority, it is achieved in the first or second session. Complications are rare. Cases of perforation are generally managed conservatively without surgical revision.

CONCLUSION

Stomal stenosis (gastrojejunal anastomotic stricture) occurs in approximately 3% to 12% of patients after RYGB and should be suspected when patients present with dysphagia, nausea, and vomiting. Endoscopic dilation of stomal stenosis *via* through-the-scope balloon dilation or wire-guided bougie dilation is safe and highly effective, and should be considered the primary treatment for this complication. Most patients can be successfully treated with 1 or 2 sessions, and surgical revision is rarely necessary. Overaggressive dilation should be avoided in order to reduce the risk of perforation and avoid dumping symptoms.

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TOPIC HIGHLIGHT

Shigetaka Yoshinaga, MD, PhD, *Series Editor*

What are the latest developments in colorectal endoscopic submucosal dissection?

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Abstract

Endoscopic submucosal dissection (ESD) enables direct submucosal dissection so that even large early-stage gastrointestinal tumors can be resected *en bloc*. ESD has recently been applied to the colorectum since it was originally developed for use in the stomach. However, colorectal ESD is technically more difficult with an increased risk of perforation compared with gastric ESD. In addition, this procedure is seldom performed in Western countries. Consequently, further technical advances and the availability of a suitable clinical training system are required for the extensive use of colorectal ESD. In this topic highlight, we review the most recent developments in colorectal ESD.

Key words: Endoscopic submucosal dissection; Colonoscopy; Colorectum; Complication; Perforation; Training

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INTRODUCTION

Endoscopic submucosal dissection (ESD) was developed in Japan in the late 1990s to resect early gastric cancer *en bloc*[1-3]. ESD enables submucosal dissection with direct visualization of the cutting line using special electrosurgical knives, so that even large early-stage gastrointestinal tumors, with severe scarring and/or in difficult locations can be resected *en bloc*[4,5]. The primary advantages associated with *en-bloc* resection are enhanced curability and more accurate histological assessment. Accurate histological assessment is essential for predicting the risk of lymph-node metastasis following endoscopic resection of a lesion, which makes it possible to decide on the most suitable treatment strategy for each individual patient[6].

LIMITATIONS OF COLORECTAL ESD

There are several anatomical features of the colorectum, including its longer length, narrower lumen, extensive angulation and thinner walls, which make the colorectal ESD technically more difficult than gastric ESD[7-14]. As a result, colorectal ESDs are not widely performed even by Japanese endoscopists because of the greater level of technical difficulty, longer time of operation and increased risk of immediate or delayed perforations compared with colorectal endoscopic mucosal resection (EMR).

The perforation rate during the early stages of ESD development was more than 10%[11-12]. However, with advances and refinements in various instruments and devices used in colorectal ESDs and accumulated experience of the endoscopists have resulted in decreased perforation rates despite the fact that a systematic educational and clinical training system has yet to be established in Japan.

Given the extent of these ESD limitations, it should come as little or no surprise that colorectal ESDs are seldom performed in Western countries[15] except by a relatively small group of endoscopists most of whom have received specialized training in Japan.

Continued improvement by individual endoscopists in their technical skills, further advance and refinement of instruments and devices such as electricosurgical knives along with the development of even more effective submucosal injection agents and the introduction of improved traction systems should facilitate easier, faster and safer colorectal ESD procedures in the relatively near future. Establishment of a suitable clinical training system will be necessary, however, to encourage the use of colorectal ESD in Japan and elsewhere on a long-term basis.

CLINICAL TRAINING SYSTEM

Colorectal ESD has been proven safe and effective when performed by highly experienced endoscopists although this procedure is not widespread even in Japan and is seldom performed in Western countries[15,16]. The main reasons for this are that colorectal ESD is extremely challenging technically, the operation time is substantially longer than EMR, particularly for less experienced endoscopists in the initial stages of the learning curve, and the risk of perforation is considerably higher than with EMR. Unfortunately, there are no formal educational and clinical training programs for colorectal ESD in Japan at the present time. Likewise, there are no guidelines concerning the most effective training strategy for colorectal ESD with few published reports on this specific subject.

It is necessary to establish a learning curve so as to decrease the colorectal ESD complication rate. We previously reported that the experience of performing at least 50 colorectal ESDs at a number of specialized medical facilities significantly decreased the risk of complications at those facilities with an odds ratio of 0.4[8].

We recommend that a minimum of 20 gastric ESDs should be performed before first attempting colorectal ESD[10], but there is an important distinction between Japan and Western countries that should be noted here. The incidence and detection rates for early stage gastric cancer are much lower in Western countries. It is advisable, therefore, that initial colorectal ESDs undertaken by Western endoscopists should be performed in the rectum because endoscopic treatment of rectal lesions are technically less difficult with a lower risk of perforation. During such rectal ESD procedures, the use of an upper gastrointestinal endoscope is recommended because it is easier to manipulate than a conventional colonoscope. In addition, we suggest that endoscopists begin by performing colorectal ESDs on smaller lesions and less-experienced endoscopists should not attempt to perform colorectal ESDs in more challenging cases including those with larger lesions particularly lesions that are 50 mm or more in size[8] and lesions with ulceration scarring.

Appropriate professional guidance in learning to perform ESD is an important consideration in terms of the learning curve at least in the early phases of such endoscopic training[17,18]. Gastric ESDs performed in Japan under the supervision of experienced endoscopists on 30 lesions by resident endoscopists, who had already learned the basic techniques, were shown to be safe and feasible with equivalent complete resection rates and acceptable complication rates compared with gastric ESDs performed by more experienced endoscopists[17]. Sakamoto *et al*[18] showed that colorectal ESD can be performed without serious complications by trainee endoscopists under the guidance of experienced specialists. In addition, they suggested that trainee endoscopists can perform colorectal ESDs safely and independently after preparatory training and experience with 30 cases based on retrospective analysis.

NEW EQUIPMENT

Electrosurgical knives

The standard needle knife and an insulation-tipped electrosurgical knife (IT knife) (KD-610L; Olympus Co., Tokyo, Japan) were initially used in performing early gastric ESDs, but safer electrosurgical knives intended for use in the esophagus and colorectum have been developed by several Japanese endoscopists during the past decade including: Flex knife (KD-630L; Olympus)[7,14], Hook knife (KD-260R; Olympus)[19], Flush knife (DK2618JN; FUJIFILM, Saitama, Japan)[20], B-Knife™ (Zeon Medical, Tokyo, Japan)[8,9] and Mucosectom® (Pentax, Tokyo, Japan)[10]. All of these knives have been used in colorectal ESDs with varying degrees of success.

In addition to being considerably safer to use in comparison to earlier instruments, the latest electrosurgical knives feature highly functional points. In fact, several more unique electrosurgical knives have been introduced since late 2010 (Figure 1).

The first of these is a shorter, thinner needle knife with a small apical disk at the tip the Dual knife (KD-650Q: Olympus), which is an improved version of the Flex knife (Figure 1A)[21]. The latest design overcomes some of the previous problems with the Flex knife such as difficulty in adjusting knife length, frequent accumulation of debris at the knife tip during ESD and slippage of the knife tip away from the endoscopic operating field especially in cases involving scarring or loose tissues. The small disk is useful for marking and conduct-

Figure 1 Newly developed electrosurgical knives for colorectal endoscopic submucosal dissection. A: Dual knife; B: Flush knife including Ball-Tipped (BT) type; C: B-Knife BT type; D: Mucosectom 2 (thin type); E: Safe knife V; F: Clutch cutter; G: SB knife.

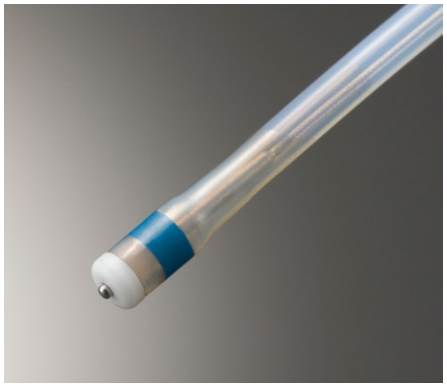

Figure 2 Dual knife in closed position.

ing hemostasis in the closed position (Figure 2) and stabilization of knife movement in the open position (Figure 1A) even in scarring and loose tissue cases. The Dual knife has two different fixed knife lengths: 2 mm for gastric ESD and 1.5 mm for esophageal and colorectal ESDs.

The Flush knife is another kind of needle knife that has the added advantage of allowing local injection. A new Flush knife with a ball-shaped tip [Flush knife ball-tipped (BT) type; DK2618JB; FUJIFILM][22] has recently been developed to improve the hemostatic function of the standard model. In addition, the ball-tip reduces the procedure time in both upper and lower gastrointestinal ESDs compared with the standard Flush knife because it facilitates scooping up incision and dissection tissues.

Finally, the B-Knife is a bipolar current knife that results in safer procedures by reducing the risk of perforations occurring during ESD. Although a ball-tipped type B-Knife had previously been developed, two tongue-type electrosurgical knives (Figure 1E and F) have also been reported as being safer to use recently[23,24]. The basic cutting technique of these knives involves grasping the mucosal or submucosal tissues and pulling back with coagulation resulting in a safer procedure although cutting speed is reduced. A report on using these knives in more difficult colorectal ESD cases is expected reasonably soon.

Submucosal injection agents

Submucosal injection solutions are used to lift lesions,

but the lengthier ESD procedure requires a longer-lasting elevation to provide direct visualization of the cutting line during dissection of the submucosal layer. Japanese endoscopists generally use glycerol, which consists of 10% glycerol and 5% fructose in normal saline solution[25], along with a small amount of indigo-carmine dye and sodium hyaluronate acid injected into the submucosal layer[26] as submucosal injection agents for colorectal ESDs. The use of these agents has resulted in safer, easier and more effective ESDs than using just normal saline.

We also have successfully demonstrated the efficacy of using CO_2 as a satisfactory submucosal injection agent during ESD procedures in preliminary animal studies[27]. An important advantage of CO_2 injection is that the increased pressure from the CO_2 produces a partial physical dissection of the fibrous submucosal connective tissues thereby making it easier to dissect the submucosal layer. Other important advantages besides its overall effectiveness are: CO_2 does not cause tissue damage, is non-allergenic, safer for patients, relatively inexpensive and commonly available worldwide. The next stage of our investigation on the effectiveness of CO_2 as a submucosal injection agent will involve a larger number of porcine models and practical clinical demonstrations.

In conclusion, the use of colorectal ESD has been proven to be both safe and highly effective in Japan when performed primarily by a selected group of highly skilled and experienced endoscopists. With further technical advances and refinements and the establishment of a suitable clinical training system required, however, before performing colorectal ESDs, colorectal ESD will become more common in clinical practice not only in Japan, but throughout the rest of the world as well.

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OBSERVATION

Possibilities of interventional endoscopic ultrasound

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Abstract

Since endoscopic ultrasound (EUS) was developed in the 1990s, EUS has become widely accepted as an imaging tool. EUS is categorized into radial and linear in design. Radial endoscopes provide cross-sectional imaging of the mediastinum, gastrointestinal tract, liver, spleen, kidney, adrenal gland, and pancreas, which has highly accuracy in the T and N staging of esophageal, lung, gastric, rectal, and pancreatic cancer. Tumor staging is common indication of radial-EUS, and EUS-staging is predictive of surgical resectability. In contrast, linear array endoscope uses a side-viewing probe and has advantages in the ability to perform EUS-guides fine needle aspiration (EUS-FNA), which has been established for cytologic diagnosis. For example, EUS-FNA arrows accurate nodal staging of esophageal cancer before surgery, which provides more accurate assessment of nodes than radial-EUS imaging alone. EUS-FNA has been also commonly used for diagnose of pancreatic diseases because of the highly accuracy than US or computed tomography. EUS and EUS-FNA has been used not only for TNM staging and cytologic diagnosis of pancreatic cancer, but also for evaluation of chronic pancreatitis, pancreatic cystic lesions, and other pancreatic masses. More recently, EUS-FNA has developed into EUS-guided fine needle injection including EUS-guided celiac plexus neurolysis, celiac plexus block, and other "interventional EUS" procedures. In this review, we have summarized the new possibilities offered by "interventional EUS".

Key words: Endoscopic ultrasound-fine needle aspiration; Interventional endoscopic ultrasound

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INTRODUCTION

Endoscopic ultrasound (EUS) was developed as a useful diagnosis modality and is used in the treatment of gastrointestinal and pancreatobiliary diseases. Since the development of EUS-guided fine needle aspiration (EUS-FNA) with a curved linear array echoendoscope, there have been many reports about the use of EUS-FNA for the treatment of various kinds of lesions. Subsequently, many authors have described other therapeutic uses for EUS, including EUS-guided biliary drainage, ethanol injection, and anti-tumor agent injection, etc., and these EUS-guided techniques have been termed "interventional EUS" procedures. In this article, we report the various

applications of interventional EUS, especially focusing on recent updates.

EUS-GUIDED BILIARY ACCESS/DRAINAGE

EUS-guided biliary drainage, which includes EUS-guided transpapillary rendezvous[1], choledochoduodenostomy[2], and hepatogastrostomy[3], has been described previously. Since endoscopic retrograde cholangiopancreatography (ERCP) is a transpapillary technique, these alternative techniques are indispensable when ERCP is unsuccessful in patients with obstructive jaundice or acute cholangitis. In 1996, Wiersema *et al*[4] first described EUS-guided cholangiography. Since then, various case studies have been reported; however, it still carries a risk of serious morbidity, including bile leakage, bleeding, or pneumoperitoneum[5,6]. In most series, the procedure has been described as follows: an echoendoscope is used, the bile duct is punctured with a 22-gauge needle under fluoroscopic guidance, and a guidewire is inserted into the bile duct. Then, a needle knife is used in incision mode under EUS guidance, and the bile duct is dilated up to 9-Fr by placing a dilator over the guidewire, before a self-expanding metallic stent is pushed through the choledochoduodenostomy site and into the extrahepatic bile duct[6]. The success rate has been reported to range from 50%-100%[7-10] in recent series, which suggests that EUS-guided biliary drainage is a feasible alternative to transpapillary drainage (Figure 1).

EUS-GUIDED PANCREATIC PSEUDOCYST DRAINAGE PROCEDURE

EUS-guided drainage has emerged as a treatment for pancreatic pseudocyst drainage, and the development of a large-channel echoendoscope has enabled it to be accomplished as a single step procedure[11]. Pancreatic pseudocysts sometimes become huge and symptomatic, and only a few cases are spontaneously resolved without effective treatment. For many years, surgical or percutaneous drainage has been the standard treatment. Recently, EUS-guided cystogastrostomy was developed and is now considered to be a feasible option for endoscopic treatment, as it is a very effective and minimally invasive approach for the management of symptomatic pancreatic pseudocysts. First, a linear echoendoscope is inserted into the stomach transorally, and pancreatic pseudocysts or fluid collections are identified. After it has been confirmed that the distance between the gastric wall and the cyst wall is less than 1 cm, a 19 G needle is inserted under EUS-guidance into the pseudocyst, and a guidewire is placed into and coiled within the pseudocyst under fluoroscopic guidance. Subsequently, the needle is retrieved, and the gastric wall is dilated with a dilator; and finally, a nasocystic drainage tube or double pig-tail tube is put in place to drain the pseudocyst into the intestine. Some high quality case reports involving this procedure have been published[12]. Varadarajulu compared the clinical outcomes of EUS-guided cystogastrostomy with surgical cystogastrostomy for the management of patients with uncomplicated pancreatic pseudocysts. There were no significant differences in success rates (100% *vs* 95%, $P = 0.36$), procedural complications (none in either cohort), or reinterventions (10% *vs* 0%, $P = 0.13$) between the surgery and EUS-guided cystogastrostomy[13]. Varadarajulu also performed a cohort study involving a total of 60 cases to evaluate the rates of technical success, treatment success, and complications and reported that the rates of technical and treatment success were 95% and 93%, respectively. The minor complication of stent migration was encountered in 1 of 60 patients (1.7%)[14]. These reports demonstrate that EUS-guided cystogastrostomy is technically feasible and is associated with a clinically similar outcome to surgical treatment.

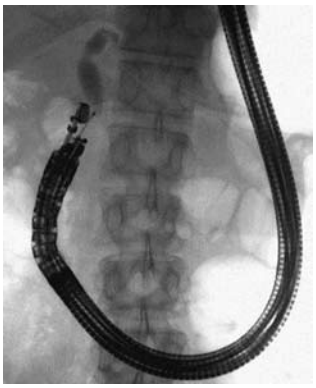

Figure 1 Endoscopic ultrasound-guided biliary drainage[5].

FORWARD-VIEWING ENDOSCOPIC ULTRASOUND FOR INTERVENTIONAL EUS

Recently, a forward-viewing curved echoendoscope, which is expected to encourage the development of novel procedural techniques for interventional EUS, has been developed as an alternative to the linear array echoendoscope. The forward-viewing curved echoendoscope was first introduced for pancreatic pseudocyst drainage in 2007[15]. Its main modifications are forward-viewing options and a curved-linear array with a narrow field of vision. However, the working channel does not have a forceps elevator. Voermans *et al*[15,16] reported that this echoendoscope has the advantage of enabling the creation of a cystogastrostomy and/or duodenostomy guided by EUS without having to puncture at an angle. The straight line configuration of the scope enables the axial application of force during needle insertion and stenting. Some cases in which the forward-viewing echoendoscope was used for pancreatic pseudocyst drainage have been reported[2,16,17]. In these cases, the pseudocyst was visualized via the forward-viewing echoendoscope with color Doppler to allow the vasculature to be avoided, and then a 19-gauge needle was inserted into the pseudocyst under EUS guidance. Alternatively,

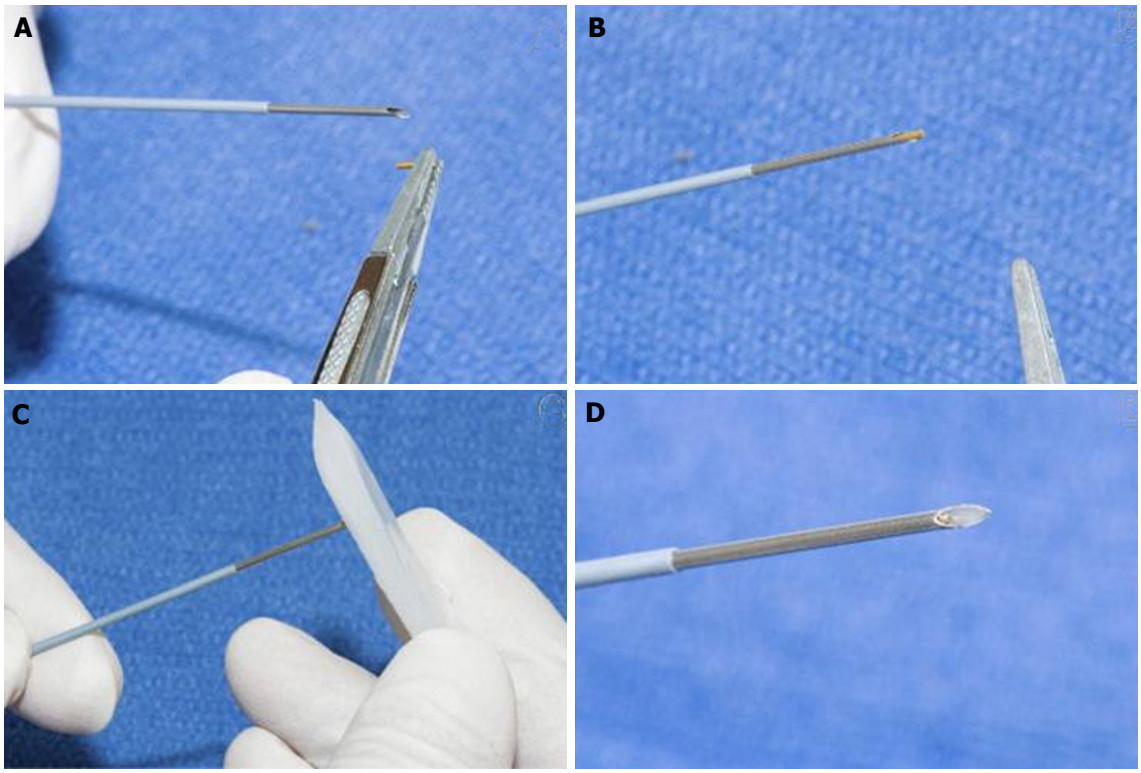

Figure 2 Endoscopic ultrasound-guided fiducial marker placement for locally advanced pancreatic cancer[22].

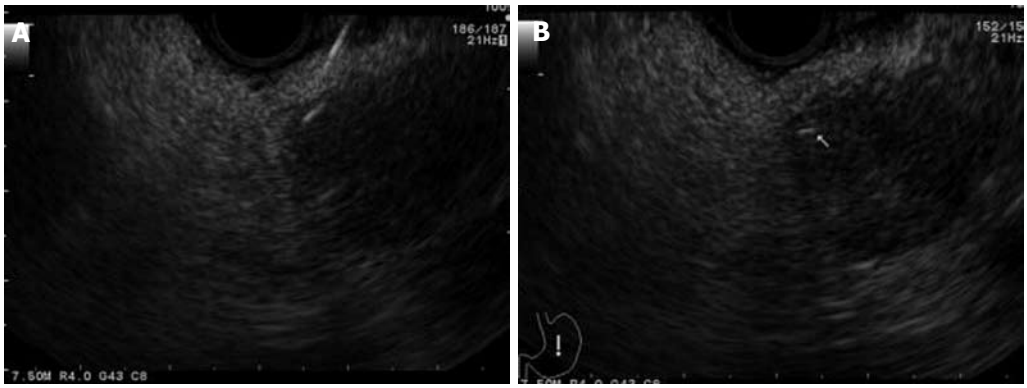

Figure 3 Endoscopic ultrasound-guided fiducial marker placement for locally advanced pancreatic cancer[22].

a technique similar to that used for cystogastrostomy with a linear array echoendoscope was employed. Since the echoendoscope and the needle are held in a straight line, the device can be maintained in the same position throughout the procedure, making it less difficult than using a linear array echoendoscope. However, the forward-viewing echoendoscope has some limitations including its narrow imaging range and the absence of a forceps elevator[18], and so further large-scale studies are needed to evaluate the forward-viewing echoendoscope.

EUS-GUIDED ONCOLOGIC INTERVENTIONS

EUS-guided fine needle injection of chemotherapeutics, fiducial marker placement, and brachytherapy have also been described. TNFrade (GenVec, Gaithersburg, Md) is an injectable agent that is injected into unresectable pancreatic tumors under EUS-guidance[19]. Then, conventional chemoradiotherapy is added to facilitate tumor death. Despite significant effectiveness being noted at 1 year, overall survival was not significantly improved. Another group reported on EUS-guided paclitaxel injection using OncoGel (ReGel/paclitaxel, BTG International, West Conshocken, PA), which resulted in the high localization of paclitaxel in the pancreas without pancreatitis[20]. The same group has also used LC beads (Biocompatibles International plc, Farnham, Surrey, United Kingdom), which are designed for the delivery of the chemotherapeutic agent irinotecan, to transport the agent into the pig pancreas. In addition, the delivery of OncoVex-GMCSF or 5-FU sustained polymer into

the pancreas has also been described[21].

Gold fiducial marker placement has been described for stereotactic body radiotherapy for locally advanced pancreatic cancer[22] or other abdominal applications, often in combination with the Cyberknife system. Pishvaian *et al*[23] reported their experiences of EUS-guided fiducial marker placement, which was successful in 84.6% of cases. In addition, a 19 gauge needle was used in previous series, and some recent reports described the use of a 22 gauge needle for fiducial placement into multiple sites; therefore, and further large series are needed to evaluate which needle is most useful for treating pancreatic cancer.

EUS-guided brachytherapy (EUS-BrTx) was first reported in 1999[24] and is still limited to small case series, which revealed that this technique results in temporary pain relief and a marginal survival benefit. EUS-BrTx is currently widely used for treating tumors in various locations such as head and neck cancer, esophageal cancer, rectal cancer, and pancreatic cancer. Sun *et al*[25] reported their experience of EUS-BrTx in a total of 15 cases of unresectable pancreatic cancer in which 11 to 33 seeds were implanted per patient. They reported a mean radioactivity of 0.89 mCi per seed and a mean total implanted activity of 20 mCi, and the treatment resulted in a partial response rate of 26.7%, a minor response rate of 20%, a stable disease rate of 33.3%, and a disease progression rate of 20%. These reports are still preliminary experiences, and further development and larger series are needed to evaluate these techniques in more detail (Figures 2 and 3).

EUS-GUIDED PANCREATIC CYST ABLATION

EUS-guided pancreatic cyst ablation using ethanol has recently been reported. In this procedure, 80%-99% ethanol is injected using an EUS-guided fine needle with or without chemotherapeutic agents. The complete cyst eradication rates are 33% to 79% at the 3 mo to 12 mo follow-up periods; however, complications, including mild pancreatitis or abdominal pain, have been reported to be associated with this procedure[26-28]. In addition, experience of this method is limited, and further evaluations are needed.

EUS-GUIDED GASTROINTESTINAL TRACT INTERVENTIONS

EUS-guided luminal anastomosis has been reported in some small studies. Fritscher-Ravens *et al*[29] reported the feasibility of EUS-guided gastrojejunostomy in a swine model. Sakamoto *et al*[30] reported on the use of endoscopic pancreaticogastrostomy reconstruction with pancreatic stent placement for pancreatic stenosis after surgery. A 19 gauge needle was inserted into the main pancreatic duct *via* the gastric wall under EUS guidance, and after guidewire placement and dilatation using a 6-Fr dilator, followed by a 5-Fr dilator, a 5 cm pancreatic stent was put in place. Kamaka *et al*[31] reported endoscopic ultrasound guided transluminal removal of gallstones. To do this, they employed EUS-guided choledochoduodenostomy; i.e., a 19 gauge needle was used to puncture the gallbladder, a 0.035-inch guidewire was placed and coiled inside the gallbladder, the gastric wall was dilated to 9-Fr using dilators, and a pig-tail type stent was deployed in the gallbladder. After 11 d, a 4 cm covered metal stent was inserted via the fistula, and the gallstones were removed *via* the choledochoduodenostomy. However, these reports are preliminary and experimental, and further clinical trials are needed; however, it has been proven that EUS-guided interventions in the gastrointestinal tract are feasible.

CONCLUSION

Most of these EUS-guided interventions are experimental. More innovations to facilitate safe EUS-guided interventions are needed including novel techniques and devices. Well-designed clinical trials are also necessary, and EUS-guided interventions could be applied to many applications in future.

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GUIDELINES FOR CLINICAL PRACTICE

Endoscopic ultrasound guided biliary drainage

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Abstract

Endoscopic retrograde cholangio-pancreatography is the most appropriate technique for treating common bile duct and pancreatic duct stenosis secondary to benign and malignant diseases. Even if the procedure is performed by skillful endoscopist, there are patients in whom endoscopic stent placement is not possible. Common causes of failure include complex peri-papillary diverticula, prior surgery procedures, tumor involvement of the papilla, biliary sphincter stenosis, and impacted stones. Percutaneous trans-hepatic biliary drainage (PTBD) and surgical intervention carry morbidity and mortality. Recently endoscopic ultrasonography-guided biliary drainage has been reported as an alternative technique. Endoscopic ultrasonography-guided biliary drainage using either direct access or a rendezvous technique has attracted attention as an alternative procedure to PTBD, with a technical success between 75%-100% and with low complication rate. We have reviewed published data on EUS guided biliary drainage procedures with the aim of summarizing the efficacy and safety of this promising method.

INTRODUCTION

Endoscopic retrograde cholangio-pancreatography (ERCP) is the most appropriate technique for treating common bile duct and pancreatic duct stenosis secondary to benign and malignant diseases. Biliary and/or pancreatic duct cannulation and visualization are successful with ERCP in a high percentage of cases managed by experienced hands. The ERCP with stent insertion in patients with malignant pancreatic-biliary strictures has a success rates between 70% to 95%[1-3]. However, even if the procedure is performed by skillful endoscopist, there are patients in whom endoscopic stent placement is not possible. Common causes of failure include complex peri-papillary diverticula, prior surgery procedures (such as gastrectomy with Billroth Ⅱ anastomosis), tumor involvement of the papilla, biliary sphincter stenosis, and impacted stones[4].

In these cases percutaneous trans-hepatic biliary drainage (PTBD) or surgical intervention is required, although both these methods carry morbidity and mortality.

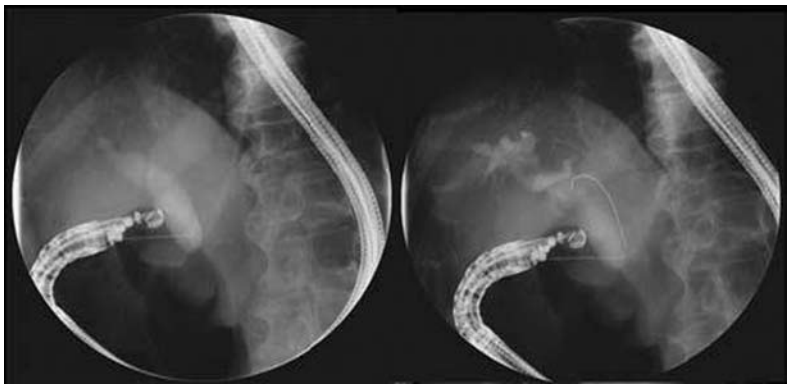

Figure 1 Cholangiogram obtained with iodine contrast injection through the endoscopic ultrasound-needle.

Some disadvantages with the percutaneous approach include the need to traverse the liver, a decreased quality of life due to the presence of external drainages and a significant morbidity and mortality, 7% and 5% respectively[4-5]. Endoscopic ultrasonography (EUS) is a widely accepted modality for the diagnosis of gastrointestinal and pancreatobiliary diseases. In 1992, Vilmann *et al*[6] published the first case report of EUS-guided fine needle aspiration (EUS-FNA) of a lesion in the pancreas head using a curved linear array echoendoscope. Since then, many researchers have expanded the indications for EUS-FNA to include various kinds of lesions, and also for therapeutic purposes. EUS-guided cholangiography was first described by Wiersema *et al*[7] in 1996. Recently endoscopic ultrasonography-guided biliary drainage has been reported as an alternative technique by many researchers[8-28]. Endoscopic ultrasonography-guided biliary drainage (EUS-BD) using either direct access or a rendezvous technique has attracted attention as an alternative procedure to PTBD, with a technical success between 75%-100% and with low complication rate[8-27].

Indeed another important advantage of EUS-BD compared with external PTBD is better quality of life due to the internal placement of the stent: this is undoubtedly a desirable goal; moreover, if allowed by local facilities, EUS-BD performed in the same session of the failed ERCP, in the same room and under the same sedation, could have many advantages for the patient and could be a rational approach also from the cost standpoint. On the other hand, the EUS guided biliary drainage, has major limitation due to fewer cases reported till date and lack of long term data. Because of, the technical difficulty encountered during re-intervention and problem of stent migration, the expertise needed for such procedure is a major limitation of the techniques. Furthermore, comparative studies of EUS-BD *vs* PTBD are required to select the optimal candidates and to best evaluate the technical and treatment outcomes also in terms of quality of life and costs.

TECHNIQUE

EUS-guided biliary drainage includes two methods: a rendezvous technique and a direct access technique, and two approach routes: trans-gastric approach and trans-duodenal approach.

Rendezvous

Once the echoendoscope is positioned in the stomach or duodenum, and the bile duct is visualized by endosonography, the bile ducts are punctured with a 19- or 22-gauge needle, bile is aspirated and iodine contrast is injected through the EUS needle to display the intra-hepatic and extra-hepatic bile ducts. Because of a standard needle has be inserted, a 2.6 mm working channel echo endoscope can be used for this procedure. After confirmation of bile duct puncture, a guide wire is advanced distally through any stricture and across the papilla using fluoroscopic guidance. When the guide wire has passed through the papilla into the duodenum, the endoscope exchange is performed: the EUS scope is removed leaving the guide wire in place and a duodenoscope is passed by the side of the EUS-placed guide wire up to the papilla. Finally, the guide wire is grasped with a snare or forceps and pulled back out the working channel of the duodenoscope for subsequent over-the-wire cannulation, the access to the common bile duct is achieved and a standard endoscopic retrograde cholangiography with stent placement can be performed.

EUS-guided choledocho-duodenostomy

The technique is basically similar to EUS-guided drainage of pancreatic pseudocyst. A EUS endoscope with large working channel is introduced, and the tip is placed in the duodenal bulb. The common bile duct is displayed from the duodenal bulb. The position is chosen based on EUS evaluation of the distance between the gastrointestinal wall and the bile duct over the stricture. A 22 G or 19 G needle is advanced and a puncture, under real time and under color Doppler assistance, is performed. After puncture, bile is aspirated and iodine contrast is injected to obtain a cholangiogram (Figure 1); a guide wire is positioned in the bile duct and a new papilla is created by precut or dilatation with catheter balloon; when a thin wire was initially used, the wire is replaced with a 0.035 inch wire. Finally, when indicated, a plastic stent is placed. The absence of intra-abdominal leakage of

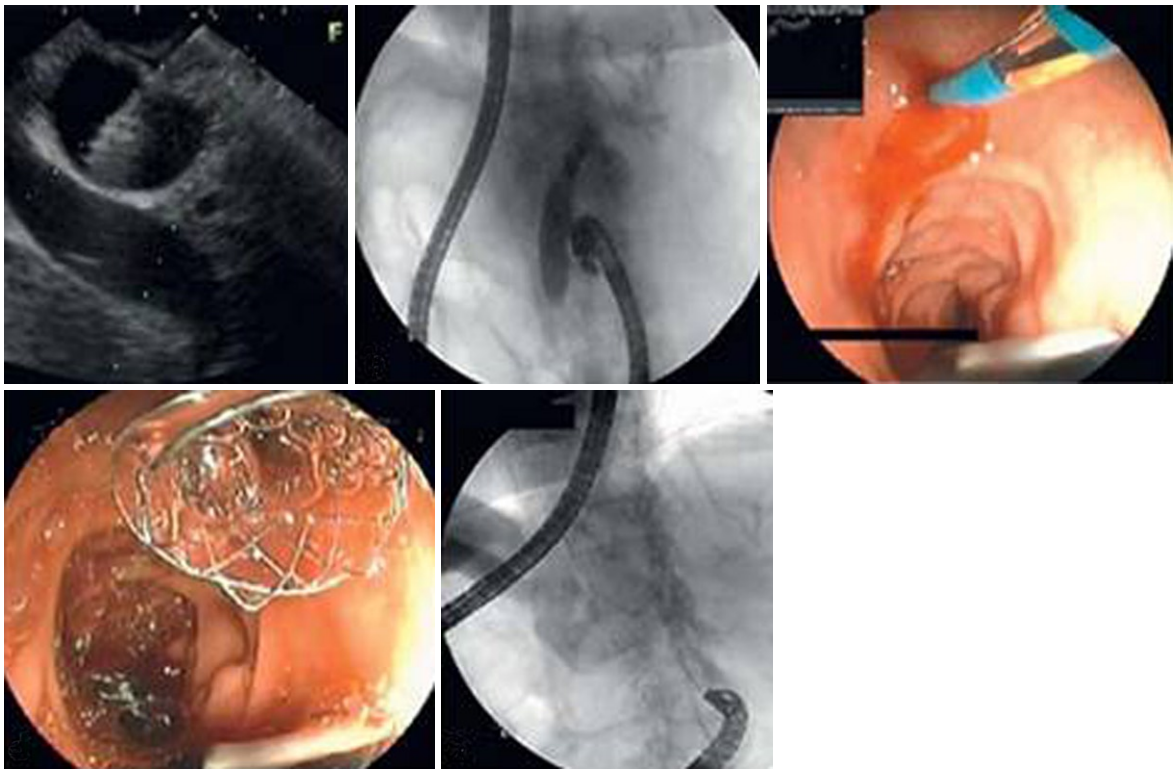

Figure 2 Covered self-expandable metallic stent placed through the choledocho-duodenostomy site into the extra-hepatic bile duct.

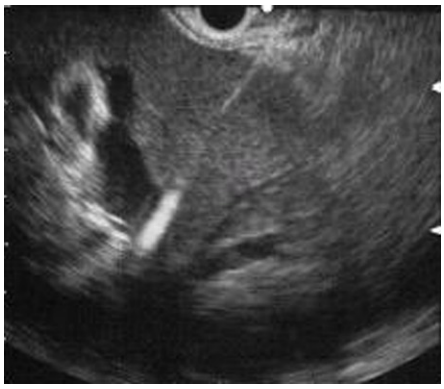

Figure 3 Puncture of the intra-hepatic duct.

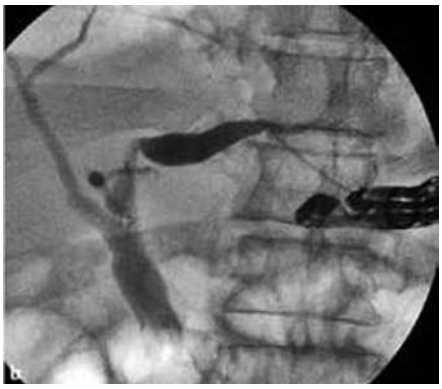

Figure 4 Puncture of the bile duct with iodine contrast injection.

contrast medium is confirmed on X-ray fluoroscopy. In recent reports, a covered self-expandable metallic stent (SEMS) instead of plastic stent is placed through the choledocho-duodenostomy site into the extra-hepatic bile duct (Figure 2). In case of stent occlusion a guide wire is inserted into the bile duct through an occluded stent using an ERCP catheter, the stent is then removed using a snare, keeping the guide wire in place. Finally, a new stent is inserted over the guide wire.

REVIEW OF LITERATURE

Rendezvous

In six reports[9,11,12,17,23,26] on EUS-guided rendezvous technique describing a total of 45 patients, the overall success rate was 80% (36/45). The complication rate was 4% (2/45), including pneumoperitoneum and bile leakage. In a recent largest case series reported by Maranki *et al*[29], of the 49 patients who underwent the intra-hepatic and extrahepatic approach only using EUS-guided rendezvous technique, the overall success rate of trans-papillary stenting was 65% (32/49). A rendezvous technique is feasible only when the endoscope can be advanced to the papillary orifice for retrieval of the guide wire. The EUS-rendezvous is used solely to puncture the obstructed bile duct and pass a guide wire through the native papilla to allow subsequent ERCP. Potential advantages of EUS-rendezvous access include achievement of biliary drainage at a single session by using conventional ERCP techniques. Though the stent patency and late complications at long term follow-up of patients treated with this technique have not yet been reported in detail,

Table 1 Reports with self-expandable metallic stent placement

Authors	Cases	Technical success	Clinical success	Method	Stent used	Early complications	Late complications
Giovannini[20]	2	100%	100%	CDS 1 HGS 1	10 F PS 1 10 F PS and PCSEMS 1	---	---
Burmester *et al*[8]	4	75% (1 failure)	100%	CDS 1 HGS 1 HJS 1	8.5 F PS	---	---
Mallery *et al*[9]	2	100%	100%	RTPS 2	USEMS	---	---
Püspök *et al*[13]	6	83% (1 failure)	80% (1 failure)	CDS 4 HJS+R 1	7-10 F PS: 4 7 F PS + USEMS: 1	Cholecistitis 1	---
Ang *et al*[18]	2	100%	100%	CDS 2	7 F PS	Pneumoperitoneum 1	---
Fujita *et al*[19]	1	100%	100%	CDS 1	7 F PS	---	---
Bories *et al*[20]	11	91% (1 failure)	80%	HGS 11	7-10 F PS 7 PCSEMS 3	PS: 1 ileus and 2 occlusion SEMS: 1 biloma and 1 cholangitis due to stent shortening	SEMS: 1 migration and 2 occlusion due to tissue ingrowth
Will *et al*[17]	8	90% (1 failure)	88.9% (1 failure)	HES 1 HGS 4 HJS 1 RTPS 1	8.5 F PS 3 PCSEMS 2 USEMS 2	Slight pain 2	Cholangitis 1
Itoi *et al*[25]	4	100%	100%	CDS 4	7 F PS 3 5 F NBD 1	Peritonitis and bleeding 1	Occlusion 1
Tarantino *et al*[23]	8	100%	100%	CDS 4 RTPS 4	10 F PS	---	---
Yamao *et al*[24]	5	100%	100%	CDS 5	7-8.5 F PS	Pneumoperitoneum 1	Migration 1 Occlusion 5
Kahaleh and Maranki *et al*[10,12,16,29]	49	84% (8 failure)	98%	TPSA 32 SIAS 1 HGS 4 CDS 4	10 F PS USEMS	Pneumoperitoneum 4 Bleeding 1 Biliary peritonitis 1 Abdominal pain 1 Aspiration pneumonia 1	Occlusion 1
Hanada *et al*[27]	4	100%	100%	CDS 4	6-7 F PS	---	---
Brauer *et al*	12	92% (1 failure)	72%	CDS 4 RTPS 7	10 F PS 5 USEMS 6	Duodenal perforation 1 Respiratory failure 1	---
Park *et al*[28]	14	100%	100%	CDS 5 HGS 9	FCSEMS	Pneumoperitoneum 2	Migration 1
Lai *et al*[32]	1	100%	100%	CDS 1	10 F PS	----	----
Martins *et al*[33]	1	100%	100%	HGS	PCSEMS	----	Migration 1 (dead)
Park *et al*[34]	5	100%	100%	HGS	FCSEMS	---	---
Nguyen-Tang *et al*[35]	5	100%	100%	TPSA	USEMS	---	---
Kim *et al*[26]	15	80% (3 failure)	100%	RTPS	USEMS 8 10 F PS 4	---	---
Belletrutti *et al*[36]	1	100%	100%	CDS	FCSEMS	---	---
Iwamuro *et al*[37]	7	100%	72%	CDS	10 F PS	Peritonitis 2	Occlusion 2
Eum *et al*[34]	3	100%	100%	CDS 2 HGS 1	FCSEMS	---	---
Artifon *et al*[38]	3	100%	100%	CDS	PCSEMS	---	---
Artifon *et al*[39]	1	100%	100%	CA	PCSEMS	---	---
Siddiqui *et al*[40]	8	100%	88%	CDS	FCSEMS	Duodenal perforation 1	---
Fabbri *et al*[31]	16	75% (4 failure)	100%	CDS 9 RTPS 3	PCSEMS	Pneumoperitoneum 1	---

SEMS: Self-expandable metallic stent.

those result seem to be basically the same as those of endoscopic trans-papillary biliary stent placement.

EUS-guided choledocho-duodenostomy

EUS guided choledocho-duodenostomy was first reported by Giovannini in 2001. Several studies have evaluated the role of EUS-CDS[8,12,13,18,19,23,25,27-30]. In these studies there are many differences in terms of type of devices used to create the fistula: needle knife or sphinterotome, 19 G or 22 G needles or needles followed by a needle knife. In 94% of cases the transduodenal stents were successfully inserted. The rate of treatment success was 100% among the patients with successful bile duct access. Theoretically one-step method with direct puncture of the extra-hepatic bile duct may reduce the risk of guide wire dislocation while the instruments are exchanged. The rate of complications reported was 15%, including bile peritonitis and pneumoperitoneum. Park *et al*[28] reported 5 cases of EUS-BD puncture with one-step placement of a fully covered SEMS. Although the follow-up periods were short (median, 6 mo; range, 2-7 mo), there was only one re-intervention necessitated by stent migration. So a longer stent patency using a fully covered metal stent can be expected. After that, sev-

eral reports on choledocho-duodenostomy with SEMS placement were published, even if with a small number and with a short follow up[31-40]. More recently Fabbri *et al*[31] reported a series of 16 patients treated with SEMS (9 choledocho-duodenostomies with SEMS placement and 3 biliary rendezvous procedures with papillary SEMS placement). No major complications and no procedure-related deaths occurred. There was one case of pneumoperitoneum which was managed conservatively. The median follow-up was 170 d. None of the patients required endoscopic re-intervention. This series demonstrated that EUS-BD with a partially covered SEMS has a high rate of clinical success and low complication rates, and could represent an alternative choice for biliary decompression.

EUS-guided hepatico-gastrostomy

EUS-guided hepaticogastrostomy was first reported by Burmester *et al*[8] in 2003. A dilated peripheral branch of the left intra-hepatic system that is closest to the EUS transducer is accessed trans-gastrically using a 19- or 22-gauge needle or a needle knife. In the same way of choledocho-duodenostomy, after removal of the needle stylet, bile is aspirated and contrast is injected to visualize the ducts under fluoroscopy (Figures 3 and 4). A guide wire is then passed through the FNA needle into the left intra-hepatic system. The wire should be positioned deep into the peripheral intra hepatic bile ducts, or should pass into the duodenum across the biliary stricture. The trans-mural tract between the stomach and the left intra-hepatic system can be dilated using either an ERCP cannula, cystotome, bougie or dilating balloon, if necessary. Finally a plastic or metallic stent is inserted though the hepatico-gastrostomy site into intrahepatic bile ducts

Review literature

Six reports are available on EUS-guided hepatico-gastrostomy[8,12,20,17,22,28]. The procedure was successful in 96% of cases (all but one case). Various types of stents, including plastic stents, uncovered metal stents, and covered metal stents were used. Once the stents were placed, all but one patient (96%) had clinical success (resolution of obstructive jaundice). The rate of complications was 14% without mortality: 1 case of ileus probably due to the use of morphine during anesthesia, 1 case of biloma, and 2 cases of cholangitis. Stent migration has been reported as a late complication in one case.

CONCLUSION

EUS continues to evolve with a new emphasis on image guided intervention rather than image analysis. The development of the large channel linear array echoendoscope allows more therapeutic procedures. Placing guide wires with EUS shows great promise in fostering endoscopy based therapy, and internal drainage of obstructed bile ducts using the EUS method is becoming accepted where ERCP fails (e.g., intra-diverticular papilla, Roux-en-Y gastrojejunostomy or other previous surgery procedure, papilla stenosis, impacted stones, *etc*,). This procedure should be limited to facilities with extensive experience in therapeutic EUS and should be used only when attempts at decompression *via* ERCP are unsuccessful. The use of this technique has already been endorsed by several studies confirming the feasibility and safety of EUS−guided procedures, including many reports with SEMS placements (Table 1). Comparative trials between EUS-guided biliary drainage versus PTBD are lacking as well as rendezvous technique versus direct access technique. Finally, as more experience is gained, we have to determine which of the following are more effective than their alternatives: transduodenal, transgastric approach, rendezvous or direct access, plastic stent or SEMS. EUS biliary drainage is not be considered as a routine procedure. Additional studies to define risks and long-term outcomes are necessary before introducing these techniques in clinical practice.

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REVIEW

Endoscopic management of esophageal varices

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Abstract

The rupture of gastric varices results in variceal hemorrhage, which is one the most lethal complications of cirrhosis. Endoscopic therapies for varices aim to reduce variceal wall tension by obliteration of the varix. The two principal methods available for esophageal varices are endoscopic sclerotherapy (EST) and band ligation (EBL). The advantages of EST are that it is cheap and easy to use, and the injection catheter fits through the working channel of a diagnostic gastroscope. Endoscopic variceal ligation obliterates varices by causing mechanical strangulation with rubber bands. The following review aims to describe the utility of EBL and EST in different situations, such as acute bleeding, primary and secondary prophylaxis

Key words: Endoscopy; Gastrointestinal bleeding; Portal hypertension; Prophylaxis; Esophageal varices

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INTRODUCTION

Portal hypertension is a common clinical syndrome, defined by a pathologic increase in the portal venous pressure, in which the hepatic venous pressure gradient (HVPG) is increased above normal values (1-5 mmHg). In cirrhosis, portal hypertension results from the combination of increased intrahepatic vascular resistance and increased blood flow through the portal venous system. When the HVPG rises above 10 mmHg, complications of portal hypertension can arise. Therefore, this value represents the threshold for defining portal hypertension as being clinically significant and plays a crucial role in the transition from the preclinical to the clinical phase of the disease[1-3].

The importance of this syndrome is characterized by the frequency and severity of complications, such as massive upper gastrointestinal bleeding from ruptured gastroesophageal varices and portal hypertensive gastropathy, ascites, hepatorenal syndrome and hepatic encephalopathy[4]. These complications are major causes of death and the main indications for liver transplantation in patients with cirrhosis.

CLINICAL COURSE OF VARICEAL BLEEDING

Portal hypertension causes the development of portosystemic collaterals, among which esophageal and gastric

varices are the most relevant[5]. Their rupture can result in variceal hemorrhage, which is one the most lethal complications of cirrhosis.

Prospective studies have shown that more than 90% of cirrhotic patients develop esophageal varices sometime in their lifetime and 30% of these will bleed. When cirrhosis is diagnosed, varices are present in about 30%-40% of compensated patients and 60% of those who present ascites[6]. After initial diagnosis of cirrhosis, the expected incidence of newly developed varices is about 5% per year[7-11].

Once developed, varices increase in size from small to large before they eventually rupture and bleed. Studies assessing the progression from small to large varices are controversial, showing the rates of progression of varices ranging from 5% to 30% per year[8,10-13]. The most likely reason for such variability is the different selection of patients and follow-up endoscopic schedule across studies[14]. Moreover, inter- observer variability also accounts for differences in the reported rates of development of varices. Decompensated cirrhosis (Child B/C), alcoholic etiology of cirrhosis, HVPG and the presence of red wale markings in the esophageal varices at the time of baseline endoscopy are the main factors associated with the progression from small to large varices[8,12,15].

Once varices have been diagnosed, the overall annual incidence of variceal bleeding accounts for 10%-15% in non-selected patients[16,17]. The most important predictive factors are variceal size, severity of liver dysfunction defined by the Child-Pugh classification and red wale markings[17]. These risk indicators have been combined in the North Italian Endoscopy Club (NIEC) index, which allows the classifications of patients into different groups with a predicted 1-year bleeding risk. According to the NIEC index, patients with small varices and advanced liver insufficiency carry a considerable risk of first bleeding. The estimated probability of bleeding within 1 year in Child-Pugh class A patients with large varices and red signs is 24%, compared with 20% for Child-Pugh C patients with small varices and no red signs. Overall, variceal size remains the most useful predictor for variceal bleeding[18]. The risk of bleeding is very low (1%-2%) in patients without varices at the first examination, and increases to 5% per year in those with small varices, and to 15% per year in those with medium or large varices at diagnosis[10,11]. Other predictors of variceal first bleeding are the presence of red signs. Variceal size and red color signs are associated with an increased bleeding risk probably because they reflect direct parameters determining variceal wall tension (radius, wall thickness), which is the decisive factor determining variceal rupture[19,20]. In addition, many studies have shown that variceal bleeding only occurs if the HVPG reaches a threshold value of 12 mmHg. Conversely, if the HVPG is substantially reduced (below 12 mmHg or by > 20% of the baseline levels), there is a marked reduction not only in the risk of bleeding, but in the risk of developing ascites, spontaneous bacterial peritonitis[21] and death.

Variceal bleeding is the most severe complication of cirrhosis and is the second most common cause of mortality among the patients[22]. In patients with cirrhosis, ruptured esophageal varices cause approximately 70% of all upper digestive bleeding[23]. Mortality from variceal bleeding has greatly decreased in the last two decades from 42% in the Graham and Smith study in 1981[24] to the actual rates that range 6-12%[10,25]. This decrease results from the implementation of effective treatment options, such as endoscopic and pharmacological therapies and transjugular intrahepatic portosystemic shunt (TIPS), as well as improved general medical care. The general consensus is that any death occurring within 6 wk from hospital admission for variceal bleeding should be considered as a bleeding-related death[26]. Immediate mortality from uncontrolled bleeding ranges from 4% to 8%[9,27-29]. Prehospital mortality from variceal bleeding is around 3%[30]. Nowadays, the patients die due to infection, kidney failure, hepaticencephalopathy, early rebleeding, or uncontrolled bleeding in the first weeks after an initial episode. The first three ones are the most important late prognostic markers after the first episode of bleeding[31]. Factors independently associated with a higher mortality are poor liver function, severe portal hypertension with HVPG > 20 mmHg, and active bleeding at endoscopy[32,33]

The natural history of esophageal varices in Non-Cirrhotic Portal Hypertension (NCPH) is not known. Progression of variceal size occurs at a rate of 10%-15% per year in patients with cirrhosis, mostly dependent on liver dysfunction. Such a progression of varices in NCPH is less likely to occur, as the liver function continues to be normal. Similarly, a decrease in the size of esophageal varices, as seen in patients with cirrhosis with an improvement in liver function, is unlikely in NCPH[34-37].

ENDOSCOPIC MANAGEMENT OF ESOPHAGEAL VARICES

Endoscopic therapies for varices aim to reduce variceal wall tension by obliteration of the varix. The two principal methods available for esophageal varices are endoscopic sclerotherapy (EST) and band ligation (EBL). Endoscopic therapy is a local treatment that has no effect on the pathophysiological mechanisms that lead to portal hypertension and variceal rupture. However, a spontaneous decrease in HVPG occurs in around 30% of patients treated with either EST or EBL to prevent variceal rebleeding[38,39]. It has been shown that patients with such a spontaneous hemodynamic response require fewer sessions of endoscopic therapy until variceal obliteration, and have a higher rate of variceal eradication than patients treated with endoscopic methods who have no spontaneous response[38,39]. Furthermore, spontaneous responders have a significantly lower probability of rebleeding and better survival. These data suggest that adding beta-blockers to endoscopic therapy may en-

hance the efficacy of treatment by increasing the rate of hemodynamic responders[39,40]

SCLEROTHERAPY

Endoscopic injection sclerotherapy has been used to treat variceal hemorrhage for about 50 years. Endoscopic treatment of bleeding esophageal varices was originally described by Crafood and Frenckner in 1939[41], though the technique was not widely adopted until the 1970s. In the 1980s, flexible endoscopic sclerotherapy replaced the methods that used rigid endoscopes, and rapid progress has been made in the techniques since then[42]. As a result, survival of patients with hemorrhage from esophageal varices has greatly improved in the last 30 years[43-45]. Subsequently, some sclerosants such as sodium morrhuate, podidocanol, ethanolamine, alcohol, and sodium tetradecyl sulfate have been widely used. Actually, the most commonly used agents are ethanolamine oleate (5%) or polidocanol (1%-2%) in Europe, and sodium morrhuate (5%) in the United States[39,46]. All these sclerosing agents have been used successfully in controlled trials[47]. Although some studies tried to compare the effectiveness between different sclerosants[48], it is difficult to draw a final conclusion.

EST consists of the injection of a sclerosing agent into the variceal lumen or adjacent to the varix, with flexible catheter with a needle tip, inducing thrombosis of the vessel and inflammation of the surrounding tissues[49,50]. During active bleeding, sclerotherapy may achieve hemostasis, inducing variceal thrombosis and external compression by tissue edema. With repeated sessions, the inflammation of the vascular wall and surrounding tissues leads to fibrosis, resulting in variceal obliteration[51]. Furthermore, vascular thrombosis may induce ulcers that also heal, inducing fibrosis. There are technical variations in performing EST, such as type and concentration of the sclerosants, volume injected, interval between sessions, and number of sessions[47]. Some endoscopists use free-hand injections, others prefer to incorporate a balloon onto the distal end of the endoscope to compress the varices following injections[52,53]. The optimal dose of sclerosants is also unknown. The sclerosants can be injected either intravariceally or paravariceally[29]. Paravariceal injection using a large volume of polidocanol, in mediately adjacent and slightly distal to the bleeding point, forms a protective fibrosis layer around varices. Intravariceal injection, directly induces variceal thrombosis. The first injection of 1-3 mL of the sclerosant should be administrated right below the bleeding site. Afterwards, 2-3 mL injections are administrated to the remaining varices adjacent to the bleeding varix. The main objective is to target the lower esophagus near the gastroesophageal (GE) junction. Up to 10-15 mL of a sclerosant solution may be used in the session. In the acute setting, the paravariceal injection cannot be easily accomplished because of the ongoing bleeding and it is mostly reserved for elective sclerotherapy[29,54].

The advantages of EST are that it is cheap and easy to use, the injection catheter fits through the working channel of a diagnostic gastroscope, it can be quickly assembled, and does not require a second oral intubation. Additionally, there is a rapid thrombosis.

However, several local and systemic complications may arise after EST[52,55-58]. The reported frequency of complications of sclerotherapy varies greatly between series and is critically related to the experience of operators and the frequency and completeness of follow-up examinations. Minor complications occurring within the first 24-48 h and not requiring treatment, such as low-grade fever, retrosternal chest pain, temporary dysphagia, asymptomatic pleural effusions, and other nonspecific transient chest radiographic changes, are very common[49].

The complications can be classified as local: esophageal ulcers, ulcer bleeding, and esophageal stricture; cardiovascular and respiratory: pleural effusion, adult respiratory distress syndrome, and pericarditis; and systemic: fever, bacteremia, spontaneous bacterial peritonitis, distant embolism, and distant abscess[53]. It is impossible to predict what kind of complications may be encountered in patients receiving EST.

Among them, bacteremia, post-sclerotherapy esophageal ulcer bleeding, and stricture are the most frequent adverse events[52,55-58]. The main cause of these hazardous complications is usually an extensive wall necrosis induced by an incorrect injection technique, too much sclerosant being injected, or a high concentration of the sclerosant[59]. Esophageal ulcers are common and they may cause bleeding in 20% of patients[60,61]. Mucosal ulceration is the most common esophageal complication, occurring in up to 90% of patients within 24 h of injection and heals rapidly in most cases. Many authors question whether ulceration should be regarded as a complication or, rather, as a desired effect of sclerotherapy, because the development of scar tissue after ulceration helps obliterate varices[62]. Nevertheless, ulcerated variceal columns found at follow-up endoscopy should not be injected. The usefulness of sucralfate in healing esophageal ulcers and preventing rebleeding is controversial[63]. They usually heal with omeprazole. Bacteremia may occur in up to 35% and lead to other complications, such as spontaneous bacterial peritonitis or distal abscesses[64,65]. Esophageal stenoses have been reported with a frequency varying between 2% and 10%. Esophageal perforation is a rare, but severe complication that may occur either by direct traumatic rupture or by full-thickness esophageal wall necrosis secondary to excessive injection of sclerosant. The former presents shortly after the procedure and may be accompanied by subcutaneous emphysema, whereas the latter may produce insidious symptoms over a few days before free perforation becomes manifest[49].

Mortality directly resulting from post-EST complications may be noted in 2% of patients and it commonly results from the major complications of recurrent bleeding, perforation, sepsis, and respiratory disorders[55]

ENDOSCOPIC VARICEAL LIGATION

In 1989, Stiegmann and Goff[66] introduced the application of endoscopic variceal ligation (EVL) to treat esophageal varices. In contrast to the use of chemical action induced by EST, EVL obliterates varices by causing mechanical strangulation with rubber bands. The technique is an adaptation of that applied to banding ligation of internal hemorrhoids. Owing to its action on the suctioned, entrapped varices, the main reaction is usually limited over the superficial esophageal mucosa.

EVL consists of the placement of rubber rings on variceal columns which are sucked into a plastic hollow cylinder attached to the tip of the endoscope[67]. Multiple-shot devices have largely replaced the original single-shot ligators, since the procedure is much simpler and faster with multishot devices, and an overtube is not required, thus avoiding the severe complications related to its use. Furthermore, new transparent caps are available which improve the visibility (visibility with the old caps may be reduced by 30%)[39]. Several commercial multiband devices are available for EBL. They have 4-10 preloaded bands. All have the same principle. i.e., placement of elastic bands on a varix after it is sucked into a clear plastic cylinder attached to the tip of the endoscope[54].

After the diagnostic endoscopy is performed and the culprit varix identified and its distance measured to the mouth, the endoscope is withdrawn and the ligation device is loaded[54]. The device is firmly attached to the scope and placed in a neutral mode. Sometimes passing the endoscope with the loading device may be tricky. This requires slight flexion of the neck, gentle and constant advancement of the scope with visualization of the pharynx, and a slight torque of the shaft left and right[54]. After intubation, the device is placed in "forward only" mode. Once the varix is identified, the tip is pointed toward it and continuous suction applied so it can fill the cap. This requires smooth movement right and left. Once inside the cap, a "red out" sign should appear and at this point the band can be fired[54]. Usually the procedure is performed by starting the application of the bands at the gastroesophageal junction and working upwards in a helical fashion to avoid circumferential placement of bands at the same level[49]. The application of bands progresses for approximately 6-8 cm within the palisade and perforating zones[53].

In the setting of an active bleed, the restricted field of vision caused by the cylinder attachment makes the technique difficult to perform and this requires active flushing with water and suction as necessary. Ideally, the rubber band should be delivered on the varix at the point of bleeding site but if missed, banding of mucosa is not harmful in contrast to injecting a sclerosant, which may cause side effects. If, however the point of bleeding cannot be identified, a multiple banding device can be used to place several bands at the GE junction, provided that no subcardial prolongation occurs, which may reduce torrential bleeding, and further bands can be fired afterward[54,59].

After the application of rubber bands over esophageal varices, the ligated tissues with rubber bands may fall off within a few days (range: 1-10 d). Following the sloughing of varices, shallow esophageal ulcers are ubiquitous at ligated sites and esophageal varices become smaller in diameter. The ligation induced-ulcers are shallower, have a greater surface area, and heal more rapidly than those caused by EST[53,68]. Patients should start with liquids for the first 12 h and then take soft foods gradually. A recent controlled trial demonstrates that subjects who received pantoprazole after elective EVL had significantly smaller post-banding ulcers on follow-up endoscopy than subjects who received placebo. However, the total ulcer number and patient symptoms were not different between the groups[69].

Eradication of varices usually requires two to four EVL sessions[39]. In a meta-analysis including 13 articles performed in 1999 by de Franchis and Primignani[49], the mean number of sessions required to achieve variceal obliteration was reduced from 3.6 in patients receiving EVL to 5.4 in patients receiving ETS. Both the optimal number of bands placed in each session and the optimal time interval between sessions should be clarified to improve the efficacy of this treatment. Usually varices are considered eradicated when they have either disappeared or cannot be grasped and banded by the ligator[39]. Variceal eradication is obtained in about 90% of patients, although recurrence is not uncommon[70]. The main disadvantage of EVL is possibly a higher frequency of recurrent varices[71-73]. Fortunately, those recurrent varices can usually be treated with repeated ligation[73]. Moreover, the recurrence after EVL did not lead to a higher risk of rebleeding or require more endoscopic treatments[53]. The optimal surveillance program should also be established. A study from Japan demonstrated that EVL performed once every 2 mo was better than EVL performed once every 2 wk regarding overall rates of variceal recurrence[74]. Because the rebleeding rate of patients receiving endoscopic therapy could only be significantly reduced in those who achieve variceal obliteration within a short period, EVL performed at an interval of 2 mo in the prevention of variceal rebleeding may be inappropriate. In our clinical pathway, sessions are scheduled at a 4-week interval to achieve variceal eradication[29].

EBL was developed as an alternative, with fewer complications than EST, for the treatment of esophageal varices. The complications of EVL include esophageal laceration or perforation (mostly due to trauma of the overtube), transient dysphagia, retrosternal pain, esophageal stricture, transient accentuation of portal hypertensive gastropathy, ulcer bleeding, and bacteremia[75]. The incidence of bacteremia and infectious sequelae after EIS was 5-10 times higher than after EVL[76].

OTHER TECHNIQUES

Argon plasma coagulation has also been combined with EVL to prevent variceal recurrence. Recently, Harras *et*

al[77] conducted a randomized trial and they established that band ligation plus argon plasmacoagulation allows for very rapid eradication of varices, and a low recurrence rate, with no obvious recorded complications, but it has the disadvantage of being the most expensive technique and requires special equipment that is only available in a few endoscopic centers.

Endoscopic clipping has been rarely guided in the management of bleeding varices. In 2003, Yol *et al*[78,79] carried out a controlled trial to evaluate the effectiveness of endoscopic clipping in the hemostasis of bleeding esophageal varices and the eventual variceal eradication was compared with that of band ligation in patients with bleeding from esophageal varices. They concluded that it results in a high initial hemostasis rate, a decreased risk of rebleeding, and fewer treatment sessions needed for variceal eradication.

The tissue adhesives n-butyl-2-cyanoacrylate (Histoacryl) and isobutyl-2-cyanoacrylate (Bucrylate) have been used to treat esophageal and gastric varices[80-82]. When injected into esophageal or gastric varices, almost immediate obliteration of the vessel was achieved. The polymerization does not depend on clotting factors. The adhesives harden within seconds of coming into contact with a physiologic milieu, forming a solid cast of the injected vessel. Thus, their injection, if executed correctly, should result in almost immediate control of bleeding as the lumen of the varix is occluded. The rapid hardening of the adhesives makes their application less simple than that of conventional sclerosants. The technique requires care to ensure that the adhesive does not come into contact with the endoscope because this might result in permanent damage to the working channel of the instrument. This risk can be minimized by applying silicone oil to the tip of the endoscope and by mixing the adhesive with a radiographic contrast agent (Lipiodol) in a ratio of 1:1 to delay the premature hardening that it occurs after 20 s[49,81]. Once correct placement has been confirmed, the tissue adhesive is injected in small aliquots of a maximum of 0.5 mL for esophageal varices and 1 mL for gastric varices. The injection of tissue adhesive differs from conventional sclerotherapy in that the injection must be strictly intravariceal. There is no consensus on the cyanoacrylate injection (CI) technique, with major variations in relation to the proportion and volume of cyanoacrylate and Lipiodol solution to be injected[83,84]. Several weeks later (2 wk to 3 mo) the overlying mucosa sloughs off and a glue cast is extruded into the lumen of the gastrointestinal tract. The ulceration subsequently reepithelialises. There are several randomized controlled trials comparing use of cyanocrilate with other therapies for treatment of esophageal varices. Evrard *et al*[85] compared CI in esophageal varices with B-blocker as secondary prophylaxis for variceal bleeding and concluded that the CI group had more complications. Another study compared CI with EVL in the treatment of variceal bleeding and variceal eradication. Despite a comparable initial success in acute bleeding control, EVL was superior to CI in the subsequent management of EVL[86]. Moreover, recently Santos *et al*[87] observed that no significant differences between the EVL and CI groups were observed in the treatment of EV inpatients with advanced liver disease regarding mortality, variceal eradication, and rates of major complications. However, minor complications and variceal recurrence were significantly more common in the CI group. In addition, there was a clear trend toward more bleeding episodes in patients included in the CI group. Based on these studies, further controlled studies are needed to recommend the injection as first-line therapy for both acute episodes and in primary and secondary prophylaxis. Complications associated with injection of cyanoacrylate glue for treatment of bleeding lesions include embolic events and equipment damage. Life threatening complications have included episodes of abdominal, pulmonary, and intracerebral embolization and infarction.

Also, detachable nylon mini-loops have been tested as an alternative for endoscopic band ligation to treat both esophageal[88,89] and gastric varices. As with band ligation, a detachable nylon ring (mini-loop), with a maximum diameter of 11 mm, passed through the accessory channel of a standard endoscope is opened at the rim of a transparent ligation chamber attached to the instrument. By suction, a varix is brought into the chamber, the mini-loop is maneuvered over the varix, closed, and detached[49]. The procedure can be repeated several times, and multiple varices can be thus ligated with a single insertion of the endoscope. Although in 1999 Shim and colleagues demonstrated similar efficacy against EVL endoloop, this technique is now obsolete due to the superiority of EVL[90].

UTILITY OF THERAPEUTIC ENDOSCOPY IN DIFFERENT CLINICAL SITUATIONS OF ACUTE BLEEDING

Both sclerotherapy and band ligation have shown to be effective in the control of acute variceal bleeding, however EVL has become the treatment of choice for both controlling variceal hemorrhage and variceal obliteration in secondary prophylaxis.

Two meta-analyses by Franchis and Primignani[49] and Laine[91] showed that EVL is better than sclerotherapy in the initial control of bleeding, prevention of rebleeding, and is associated with less adverse events (including ulceration and stricture formation) and improved mortality. Additionally, sclerotherapy, but not EVL, may induce a sustained increase in portal pressure[92]. Therefore, EVL should be the endoscopic therapy of choice in acute variceal bleeding, though injection sclerotherapy is acceptable if band ligation is not available or technically difficult[26]. The combination of EST and EVL does not appear to be better than EVL alone[93]. Endoscopic therapy can be performed at the time of diagnostic endoscopy, early after admission, provided that a skilled

endoscopist is available. In our experience, when there is severe active bleeding, we normally use the EST, because the EVL is technically more difficult. However, when there are white nipple signs or hematocystic spots, we proceed with EVL[29].

Drug therapy (terlipressin or somatostatin) also improves the results of endoscopic treatment if started before or just after sclerotherapy or band ligation[94-97]. Vice versa, the endoscopic therapy also improves the efficacy of vasoactive treatment[94]. However, this combined approach failed to significantly improve the 6-wk mortality with respect to endoscopic therapy or a vasoactive drug[94] alone[98,99].

The current recommendation is to combine the two approaches, start vasoactive drug therapy early (ideally during the transferal to the hospital, even if active bleeding is suspected) during 5 d and perform EVL (or injection sclerotherapy if band ligation is technically difficult) after initial resuscitation when the patient is stable and bleeding has ceased or slowed[26,98].

PRIMARY PROPHYLAXIS OF ESOPHAGEAL VARICEAL BLEEDING

So far, there has been no reliable method for predicting which cirrhotic patients will have esophageal varices without endoscopy[100]. None of the above noninvasive methods is accurate enough to completely discard the presence of esophageal varices when noninvasive indicators are negative. Thus, the current recommendation is that all patients, at the time of initial diagnosis of cirrhosis, should undergo an endoscopy for the screening of esophageal varices[101].

The optimal surveillance intervals for esophageal varices have not yet been determined. In patients without varices on initial endoscopy, repeated endoscopies at 2-3 year intervals have been suggested to detect the development of varices before bleeding occurs[102]. In the centers where hepatic hemodynamic studies are available, it is advisable to measure HVPG. This interval should be decreased in patients who have an initial HVPG 10 mmHg. In patients with small varices on initial endoscopy, the aim of subsequent evaluations is to detect the progression of small to large varices because of the important prognostic and therapeutic implications. Based on the yearly progression rates of 5%-20% (a median of 12%) in the prospective studies, endoscopy should be repeated every 1-2 years[102]. In patients with advanced cirrhosis, red wale marks or alcoholic cirrhosis, a 1-year interval might be recommended. Once the patient is started on beta-adrenergic blockers, there is no need for further endoscopic surveillance.

Because of the high mortality rate associated with the initial variceal hemorrhage, primary prevention is indicated. In patients with small varices that are associated with a high risk of hemorrhage (varices with red wale marks or varices in a patient with Child class C disease), nonselective beta-blockers are recommended[26]. Patients with small varices without signs of increased risk may be treated with non-selective beta-blockers (NSBB) to prevent progression of varices and bleeding. Further studies are required to confirm their benefit[26].

In patients with medium or large varices, either nonselective beta-blockers or endoscopic variceal ligation can be used, since a meta-analysis of high-quality, randomized, controlled trials has shown equivalent efficacy and no differences in survival[103]. EST is not recommended for primary prophylaxis[55]. Meta-analysis consistently show a significantly lower incidence of first upper gastrointestinal bleeding and variceal bleeding with ligation *vs* beta-blockers[104,105]. The advantages of nonselective beta blockers are that their cost is low, no expertise is required for their application, and they may prevent other complications, such as bleeding from portal hypertensive gastropathy, ascites, and spontaneous bacterial peritonitis because they can reduce portal pressure[106,107]. The disadvantages of these agents include relatively common contraindications and side effects (fatigue and shortness of breath) that preclude treatment or lead to discontinuation in 15%-20% of patients[106]. Critics of ligation point out that although adverse events are less common with ligation, rare side effects such as ligation-induced ulcer bleeding can be much more severe than most beta-blocker-induced adverse events that are almost never fatal[108]. In most cases, beta-blocker is recommended as a first-line therapy for primary prophylaxis, with EVL being an option in patients who are intolerant to BB or in whom BB is contraindicated.

Carvedilol is a nonselective β-antagonist with α1-receptor antagonist activity, which is a promising alternative that needs to be further explored[26]. Carvedilol may be more effective than propranolol, which resulted in reduced rates of bleeding compared with EVL[109,110]. Carvedilol at low doses (6.25-12.5 mg/d) was compared with endoscopic variceal ligation in a recent randomized controlled trial. Carvedilol was associated with lower rates of first variceal hemorrhage (10% *vs* 23%) and had an acceptable side-effect profile, unlike endoscopic variceal ligation, for which compliance was low and the rate of first hemorrhage was at the upper end of the range of rates in previous studies[106].

The combination of pharmacological and endoscopic therapy was also investigated, with contrasting results. In the study of Sarin *et al*[34], endoscopic band ligation plus beta-adrenergic blockers appears to offer no benefit in terms of the prevention of first bleeding when compared with endoscopic band ligation alone.

Theoretically, isosorbidemononitrate (ISMN) might decrease portal pressure but maintain liver perfusion. However, because they are not liver specific, these agents induce arterial hypotension and elicit a reflex splanchnic vasoconstriction with a subsequent reduction in portal blood flow[37]. There are two randomized controlled trials (RCTs) published in full papers investigating the use of nitrates in monotherapy in the prevention of first variceal bleeding[111,112]. Although it was initially thought that

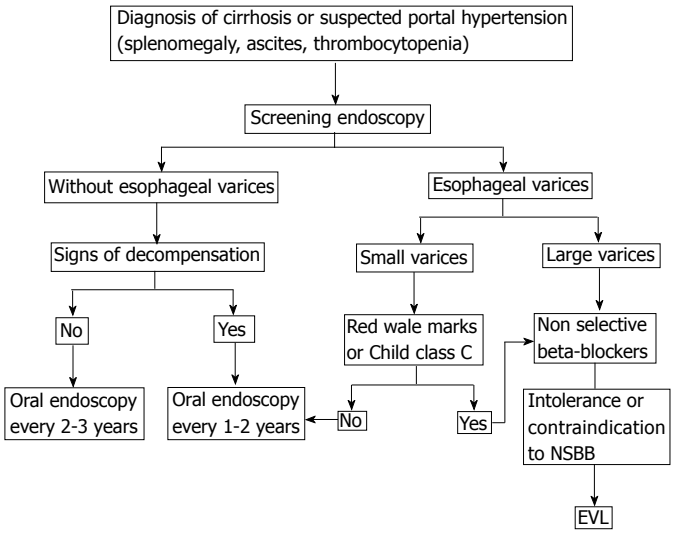

Figure 1 Primary prophylaxis of esophageal variceal bleeding. NSBB: Non-selective beta-blockers; EVL: Endoscopic variceal ligation.

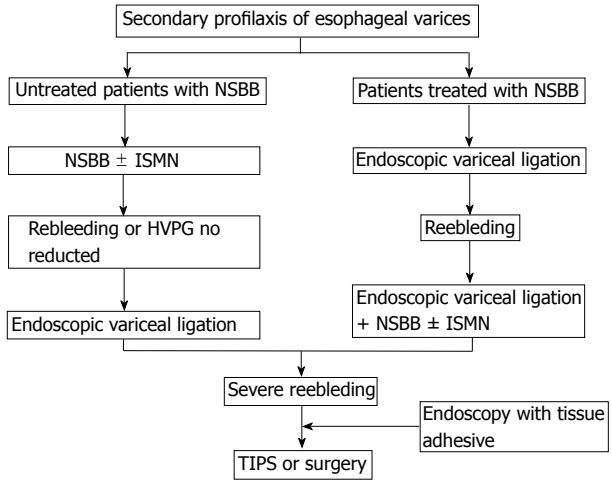

Figure 2 Secondary prophylaxis of esophageal varices. NSBB: Non-selective beta-blockers; EVL: Endoscopic variceal ligation; ISMN: Isosorbide mononitrate; TIPS: Transjugular intrahepatic portosystemic shunt.

ISMN was a safe and effective alternative to propranolol, higher mortality rates were observed in patients who received ISMN.

The choice of treatment should be based on local resources and expertise, patient preference and characteristics, side effects, and contraindications. In most cases, BB is recommended as a first-line therapy for primary prophylaxis, with EVL being an option in patients who are intolerant to BB or in whom BB is contraindicated (Figure 1).

PREVENTION OF VARICEAL REBLEEDING

Once acute bleeding is successfully controlled, rebleeding may occur in approximately two-thirds of patients if further preventive measures are not taken. Several factors have been noted to be associated with the recurrence of variceal bleeding, including portal pressure, poor liver reserve, size of varices, treatment modalities of acute bleeding, infection and portal vein thrombosis[9,28,113]. Secondary prophylaxis should start as soon as possible from day 7 of the index variceal episode.

Over the past two decades, several treatment modalities have been improved and introduced to practice with a decreased rebleeding risk and mortality. Combined pharmacological therapy (nonselective beta-blockers plus nitrates) or the combination of endoscopic variceal ligation plus drug therapy are indicated because of the high risk of recurrence, despite that the side effects are more common than in a single agent therapy (recommended for primary prophylaxis).

Both non-selective beta-blockers and EST have shown efficacy in preventing variceal rebleeding as compared with untreated controls[16,70]. However, other options have improved the results of both pharmacological and endoscopic therapy. EVL has established superiority over EST in numerous studies[49,91]. Combined therapy with beta-blockers and ISMN has been shown to be superior to beta-blockers alone and to EST[114]. The results of trials comparing combined therapy with beta-blockers plus ISMN versus EVL have shown that drug therapy is at least as effective as EVL in preventing variceal rebleeding[115-117].

A meta-analysis showed that rates of rebleeding (from all sources and from varices) are lower with a combination of endoscopic therapy plus drug therapy than with either therapy alone, but without differences in survival[118]. Another recent meta-analysis including 17 RCTs showed that combination of β-blocker and endoscopic treatment significantly reduced rebleeding rates and the mortality as compared with endoscopic treatment alone. Therefore, current guidelines recommend the combined use of endoscopic variceal ligation and nonselective beta-blockers for the prevention of recurrent variceal hemorrhage, even in patients who have had a recurrent hemorrhage despite treatment with nonselective beta-blockers or endoscopic variceal ligation for primary prophylaxis. In patients who are not candidates for endoscopic variceal ligation, the strategy would be to maximize portal pressure reduction by combining non-

selective beta-blockers plus nitrates[26,106]. Patients with cirrhosis who are contraindicated or intolerant to beta-blockers are candidates for periodical band ligation[26]. Patients who fail in the endoscopic and pharmacological treatment for the prevention of rebleeding, TIPS with polytetrafluoroethylene is the optional treatment. Covered stents are effective and are the preferred option. Also surgical shunt in Child-Pugh A and B patients is an alternative if TIPS is unavailable. Finally, transplantation provides good long-term outcomes in appropriate candidates and should be considered accordingly. TIPS may be used as a bridge to transplantation[26] (Figure 2).

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BRIEF ARTICLE

A study of the changes in the cause of peptic ulcer bleeding

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Abstract

AIM: To clarify the frequency of and changes in the cause of peptic ulcer bleeding.

METHODS: This study retrospectively evaluated the out- and inpatients who underwent endoscopy between 2002 to 2008. The subjects were patients presenting with peptic ulcer bleeding. The details of these patients were obtained from their endoscopic reports and medical records.

RESULTS: The rates of *Helicobacter pylori* (*H. pylori*) infection were significantly low (P = 0.039), while the proportion of nonsteroidal antiinflammatory drugs (NSAIDs) users and vascular disease significantly increased over the period studied (P = 0.034 and P = 0.04, respectively). However, there was no significant difference in the proportion of low-dose aspirin users (P = 0.832).

CONCLUSION: It's found that the primary cause of peptic ulcer bleeding changed from *H. pylori* infection to use of NSAIDs over the 7-year period of study. It seems that the number of low-dose aspirin users has increased with the increase in the proportion of vascular disease. It is necessary to take measures to prevent peptic ulcer bleeding among NSAIDs and low dose aspirin users.

Key words: Peptic ulcer bleeding; Gastroduodenal ulcer; *Helicobacter pylori*; Nonsteroidal antiinflammatory drugs; Low-dose aspirin

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection and the use of nonsteroidal antiinflammatory drugs (NSAIDs) are two of the major risk factors for peptic ulcers and ulcer complications[1]. *H. pylori* infection has been recognized in more than 87% of patients with gastric ulcers and about 96% of patients with duodenal ulcers[2]. The incidence of peptic ulcers has steadily decreased in Western countries, and this decrease is thought to result from both the widespread eradication of *H. pylori* and the decreasing prevalence of *H. pylori* infection in the population as a result of the improvement in hygienic conditions[3,4].

On the other hand, the use of NSAIDs is associated with an increased risk of major upper gastrointestinal complications, including bleeding and perforation[5-7]. With the increase in the elderly population, which has led to an increase in musculoskeletal and joint disorders, it seems that the consumption of NSAIDs has increased. In addition, antiplatelet therapy with low-dose aspirin (75-325 mg) reduces the risk of vascular events in patients with cardiovascular and cerebrovascular diseases[8-10]. Although low-dose aspirin has the advantages of being both highly effective and inexpensive, they pose a significant risk for developing peptic ulcer bleeding[11-13]. The aim of this study is to clarify the frequency and trends of peptic ulcer bleeding over the past seven years.

MATERIALS AND METHODS

Patients

This study retrospectively evaluated the 199 994 of out- and inpatients who underwent endoscopy at ToyamaUniversityHospital between January 2002 and December 2008. We collected the following details of patients with peptic ulcer bleeding from their endoscopic reports and medical records: age, gender, symptoms, *H. pylori* infection, NSAIDs intake, low-dose aspirin intake, previous ulcer history, cardiovascular and cerebrovascular diseases, endoscopic findings, and interventions. The rate of gastroduodenal ulcer (GDU) and peptic ulcer bleeding, average age, body proportions, hematemesis, melena, and previous ulcer histories, rate of *H. pylori* infection, rate of cardiovascular and cerebrovascular diseases and proportion of NSAIDs and low-dose aspirin users were calculated and compared from 2002 to 2008 based on this information. The subjects were checked for *H. pylori* infection using the ^{13}C-urea breath test (UBT) and/or rapid urease test (RUT). *H. pylori* status was defined as *H. pylori*-negative when UBT was negative and *H. pylori*-positive when either UBT or RUT were positive. Peptic ulcer bleeding was defined as a clinical presentation of hematemesis and/or melena, and endoscopic examination showed a peptic gastric and/or duodenal ulcer. However, we also anticipated the presence of upper gastrointestinal tract neoplasm, erosive gastritis, erosive duodenitis, Mallory-Weiss syndrome, and esophagogastricvarices.

Statistical analysis

The following details of peptic ulcer bleeding patients were obtained from their endoscopic reports and medical records: age, gender, symptoms, *H. pylori* status, NSAIDs intake, low-dose aspirin intake, previous ulcer history, endoscopic findings, and interventions. The rate of peptic ulcer and/or peptic ulcer bleeding, average age, body proportions, hematemesis, melena, previous ulcer histories, rate of *H. pylori* infection, rate of cardiovascular and cerebrovascular diseases and rate of NSAIDs, low-dose aspirin users were calculated and compared from 2002 to 2008 based on this information.

Changes in each parameter over the period studied were analyzed using the chi-square test. Differences were considered to be statistically significant when $P < 0.05$.

RESULTS

The details of subjects were showed in Table 1. The rate of GDU decreased from 16.9% to 11.3% over the period studied, and there were significant changes ($P < 0.001$). The rate of peptic ulcer bleeding significantly increased from 4.87% to 9.03% during the first three years ($P < 0.001$) and significantly decreased from 9.03% to 5.95% during the last three years ($P < 0.05$). The clinical details of those patients who presented withpeptic ulcer bleeding are shown in Table 2. Age and gender did not change significantly over the period studied. The rate of GDU decreased. Cardiovascular and cerebrovascular diseases significantly increased from 29.2% to 61.9% over the period studied ($P = 0.04$). The risk factors of peptic ulcer bleeding are shown in Table 3. *H. pylori* infection rate was 84.2% in 2002, 72.6% in 2005, and 71.4% in 2008, which demonstrates a significant decrease ($P = 0.048$). The greatest cause of peptic ulcer bleeding was the use of gastrointestinal injury drugs, such as NSAIDs and low-dose aspirin. The proportion of NSAIDs users significantly increased ($P = 0.034$), but the there were no significant changes in the proportion of low-dose aspirin users ($P = 0.832$). The proportion of NSAIDs (including low-dose aspirin) users significantly increased over the period studied ($P = 0.021$).

DISCUSSION

In this study, it was found that the number of peptic ulcer bleeding cases significantly increased during the first three years. One explanation for this is that while the *H. pylori* infection rate decreased over this period, the main cause of peptic ulcer bleeding changed from *H. pylori* infection to use of NSAIDs, including low-dose aspirin. NSAIDs were associated with approximately 30% of the bleeding peptic ulcers diagnosed in Japan, which shows a significant increase from the figures of previous reports. One reason of the increased number of NSAIDs users is that it is used in treating back and joint pain, which has shown an increased incidence among the increasing elderly population[14,15]. In the Unitd States, hospitalization and death due to NSAID-related gastrointestinal events have been estimated at 103 000 and 16 500 patients per year, respectively[16]. In a population-based retrospective case-control study, the adjusted relative risk (RR) of upper gastrointestinal bleeding (UGIB) associated with NSAIDs use was 5.3 [95% confidence interval (CI): 4.5-6.2][17]. In our study, NSAIDs use was significantly associated with an increased risk of bleeding ulcer, and the rate of *H. pylori* infection was significantly lower throughout the observed period. Nonetheless, the number of peptic ulcer bleeding was decreased during the last three years. As one of the possibilities, a

Table 1 The incidence of peptic ulcer bleeding

	2002	2005	2008
Number	2910	3023	3121
No. of GDU	493	421	353
Rate of GDU (%)	16.9	13.9	11.3
No. peptic ulcer bleeding	24	38	21
Rate of peptic ulcer bleeding (%)	4.87	9.03	5.95

The rate of GDU significantly decreased during the period studied ($P < 0.001$). The rate of peptic ulcer bleeding significantly increased during the first three years and significantly decreased during the last three years. GDU: Gastroduodenal ulcer.

Table 2 Clinical characteristics of patients with peptic ulcer bleeding

	2002	2005	2008	*P* value
Cases	24	38	21	
Age (average ± SD)	63.1 ± 17.6	69.1 ± 15.8	65.9 ± 15.2	0.738
Male *n* (%)	18 (75.0)	25 (84.8)	15 (71.4)	0.75
Gastric ulcer *n* (%)	20 (83.3)	31 (81.6)	16 (76.2)	0.824
Haematemesis *n* (%)	10 (50.0)	10 (30.3)	7 (33.3)	0.433
Melena *n* (%)	13 (65.0)	26 (78.8)	14 (66.7)	0.534
Vascular disease *n* (%)	7 (29.2)	13 (34.2)	13 (61.9)	0.048

Clinical characteristics of patients with peptic ulcer bleeding. There was significantly increased in vascular disease over the period studied.

study of the Swedish population from 1974-2002 was reported that the increasing the amount of proton pomp inhibiter (PPI) has reduced the incidence of peptic ulcer complications[18]. In fact that gastroesophageal reflux disease is increasing and the usage of PPI is actually increasing in Japan[19].

Low-dose aspirin is also one of the causes of drug-induced peptic ulcer bleeding. It is widely used because it reduces the risk of cardiovascular events and death in patients with coronary and cerebrovascular diseases. It seems likely that the number of low-dose aspirin users will increase in the future because coronary and cerebrovascular diseases have increased in recent years. However, the use of aspirin, even at a low dose for secondary prevention of cardiovascular events, remains a risk factor for developing UGIB. In addition, more than a few epidemiological studies have suggested that *H. pylori* infection increases the risk of UGIB in patients taking low-dose aspirin[20,21]. Taha et al. reported that the increase in UGIB associated with the use of gastrointestinal toxic drugs increased in subjects treated with low-dose aspirin between 1996 and 2002[22]. A recent study indicates that the relative risk of UGIB after exposure to low-dose aspirin is 3.7 (95% CI: 3.0-4.5)[17]. In our study, we found that the proportion of low-dose aspirin users also increased from 8.3% in 2002 to 14.3% in 2008. In addition, our data showed the significant increasing of cardiovascular and cerebrovascular diseases. Therefore, the proportion of low-dose aspirin users will be increased in future. Recently it was suggested that the damaging effect of

Table 3 Risk factors of peptic ulcer bleeding

	2002	2005	2008	*P* value
Helicobacter pylori *n* (%)	20/24 (83.3)	20/38 (72.6)	15/21 (71.4)	0.039
NSAIDs *n* (%)	3 (12.5)	11 (28.9)	10 (47.6)	0.034
Low-dose aspirin *n* (%)	2 (8.3)	5 (13.2)	3 (14.3)	0.832
NSAIDs and/or Low-dose aspirin *n* (%)	5 (16.7)	16 (42.1)	13 (61.9)	0.021

The *H. pylori* infection rate significantly decreased. On the other hand, the proportion of NSAIDs users was significantly increased. The proportion of low-dose aspirin users demonstrated no significant changes. NSAIDs: Non-steroidal anti-inflammatory drugs.

aspirin alone on the gastric mucosa might be less potent than the effect of NSAIDs[23]. In a case-control study by Hallas et al., the age- and sex-adjusted odds ratios associating drug use with UGIB were 1.8 (1.5-2.1) for low-dose aspirin, 1.1 (0.6-2.1) for clopidogrel, 1.9 (1.3-2.8) for dipyridamole, 1.8 (1.3-2.4) for vitamin K antagonists, 7.4 (3.5-15) for clopidogrel and aspirin, 5.3 (2.9-9.5) for vitamin K antagonists and aspirin, and 2.3 (1.7-3.3) for dipyridamole and aspirin. These results suggest that combined antithrombotic therapy with low-dose aspirin is associated with an increased risk of UGIB[24]. We also found that the proportion of NSAIDs and low-dose aspirin users was significantly increasing over the period studied. The odds ratio of a combination of NSAIDs and low-dose aspirin was reported as 12.7 (95% CI: 7.0-23.0). Furthermore, the concurrent use of non-aspirin antiplatelet agents with traditional NSAIDs also potentiated the risk of UGIB[17]. In a meta-analysis of randomized, placebo-controlled trials of low-dose aspirin, prior gastrointestinal events, older age, and the use of other injurious medications, such as NSAIDs, anticoagulants, and corticosteroids seemed to be factors associated with an increased risk for UGIB[25].

In the future, it will be necessary to prevent the association between UGIB and the use of NSAIDs and low-dose aspirin because it is expected that the more the proportion of the elderly population increases, the more coexisting diseases, such as cardiovascular disease, cerebrovascular disease, and musculoskeletal disorders will increase. The use of both NSAIDs for the treatment of musculoskeletal pain and low-dose aspirin as an antithrombotic therapy has increased recently. This tendency has been deduced from our data, which reveals that cardiovascular and cerebrovascular diseases have increased from 2002 to 2008. In addition, it is useful to note that few patients complained of epigastric symptoms in our study. In fact, most NSAIDs-associated GDU are asymptomatic[26,27]. In low-dose aspirin users, there were no significant differences between the ulcer and non-ulcer groups in the frequency and severity of symptoms, such as nausea, acid regurgitation, and heartburn[28]. Moreover, there were more patients without symptoms than with abdominal pain among NSAIDs users, since NSAIDs have an analgesic effect. On the contrary, peptic ulcers treated with NSAIDs and low-dose aspirin develop sud-

denly by hematemesis and melena. In fact, those patients taking NSAIDs and low-dose aspirin became serious cases because they had a coexisting disease, such as cardiovascular or cerebrovascular disease.

The prevention of peptic ulcers related to the use of NSAIDs and/or low-dose aspirin will become an important issue in the future. It is suggested that those patients who need NSAIDs treatment use the prostaglandin analogue misoprostol[29] or acid-suppressive agents, such as high-dose H_2 receptor antagonists[30] and PPI[31]. Switching from non-selective NSAIDs to cyclooxygenase-2 inhibitors[32] is also a choice. In the prevention of ulcers caused by NSAIDs and/or low-dose aspirin, the effectiveness of *H. pylori* eradication therapy has been reported[33]. In naive NSAIDs users, it has been suggested to receive *H. pylori* eradication therapy before NSAIDs use. A similar strategy has also been suggested for naive aspirin users[34]. In chronic NSAIDs/aspirin users, the recommendations may depend on the risk for peptic ulcer complications. Those who continue taking NSAIDs/aspirin, being at high-risk for peptic ulcer complication, should be tested for the presence of *H. pylori* infection and, if positive, receive *H. pylori* eradication therapy, as well as long-term therapy with a PPI[35-37].

Where the elderly population is increasing, it seems likely that the consumption of NSAIDs and low-dose aspirin will also increase in the future. Therefore, it is necessary to make guidelines for the use of NSAIDs and low-dose aspirin with the cooperation of gastroenterologists, neurologists, cardiologists, and orthopedic surgeons.

COMMENTS

Background

Helicobacter pylori (*H. pylori*) infection and non-steroidal anti-inflammatory drugs (NSAIDs) including low dose aspirin are two of the major risk factors for peptic ulcers. With the increase in the elderly population, which has led to an increase in musculoskeletal and joint disorders, ischemic heart disease and cerebrovascular disease, it seems that the incidence of NSAID-related peptic ulcer has increased. The aim of this study is to clarify the frequency and trends of peptic ulcer bleeding over the studied period.

Research frontiers

In Western countries, *H. pylori* infection rate is low and the cause of peptic ulcer was NSAIDs. Since the same tendency was recognized in Japan, it is necessary to investigate about changes in the cause of peptic ulcer.

Innovations and breakthroughs

In this study, it was found that the number of peptic ulcer bleeding case was increased and *H. pylori* infection rate was decreased over the studied period, the main cause of peptic ulcer bleeding changed from *H. pylori* infection to use of NSAIDs, including low-dose aspirin.

Applications

In fact that gastroesophageal reflux disease is increasing and the usage of proton pump inhibitors (PPI) is actually increasing in Japan. The results suggest that peptic ulcer will be decreased in the future.

Terminology

Peptic ulcer bleeding: Defined as a clinical presentation of hematemesis and/or melena, and endoscopic examination showed a peptic gastric and/or duodenal ulcer bleeding.

Peer review

This paper describes the rate of peptic ulcer bleeding and the change in the causes of that. Although *H. pylori*infection and the use of NSAIDs were adopted as a risk factor, it was indicated that other factors (i.e., corticosteroid, warfarin and clopidogrel) should also have been examined. Though we find that frequency on gastrointestinal bleeding has been subsequently decreasing recent years, it was reported that the increase in the usage of PPI is related. To investigate the cause by which the peptic ulcer bleeding is decreased will be desired from now on.

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CASE REPORT

Role of endoscopic ultrasound and endoscopic retrograde cholangiopancreatography in isolated pancreatic metastasis from lung cancer

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Abstract

A case is reported of a 50-year-old woman with a history of small-cell lung cancer admitted with pancreatic head lesions, discovered during investigation for obstructive jaundice. Endoscopic ultrasound assisted fine needle aspiration of the pancreatic mass was consistent with small cell carcinoma, presenting as an isolated metastasis from the previously diagnosed lung cancer. Endoscopic retrograde cholangiopancreatography (ERCP) showed extrinsic compression and a bile duct stricture, requiring sphincterotomy and stent insertion. This case highlights that acute pancreatitis and biliary obstruction can occur as a manifestation of small cell lung cancer metastasizing to the pancreas. EUS is a safe, low risk and rapid diagnostic tool in such cases, and ERCP with stenting offers a safe and effective treatment option.

Key words: Endoscopy; Endoscopic retrograde cholangiopancreatography; Endoscopic ultrasound; Lung cancer; Pancreatic lesion; Pancreatic mestastasis

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INTRODUCTION

The pancreas is a rare site for solitary metastases, but is often involved in diffuse metastatic disease[1]. The literature demonstrates that most of the patients with isolated pancreatic metastases are from renal cell cancer[2]. Our case is one of the extremely rare occurrences[3-5] of small-cell lung cancer, an infrequent form (10%) of lung cancer, metastasizing to the pancreas.

CASE REPORT

A 50-year-old Caucasian female, with a history of small-cell lung cancer post chemo-radiation, presented with vomiting, severe epigastric pain radiating to the back, and a 10 pound weight loss over a 3 mo period. She was noted to have direct hyperbilirubinemia (1.6 mg/dL, normal 0.1-0.5 mg/dL), elevated alkaline phosphatase (1147 IU, normal 32-91 IU), transaminitis (aspartate aminotransferase 242 IU, normal 15-41 IU; alanine aminotransferase 294 IU, normal 14-54 IU) and elevated lipase (274 IU, normal 22-51 IU).

Abdominal computed tomography (CT) scan (Figure 1) demonstrated distended gallbladder, intrahepatic

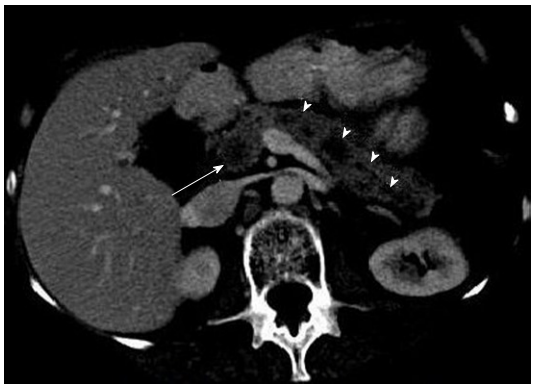

Figure 1 Computed tomography scan of the abdomen showing multiple cystic lesions throughout the pancreas (arrow heads), the largest seen in the pancreatic head (arrow).

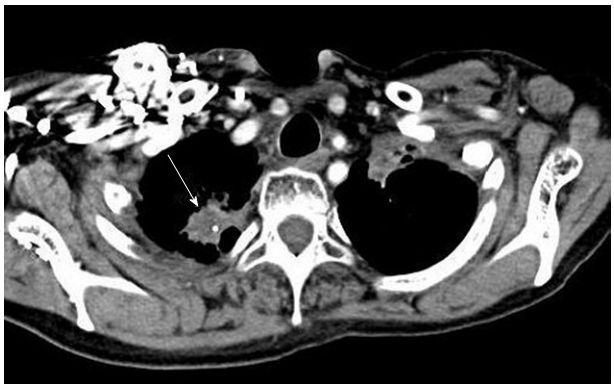

Figure 2 Computed tomography scan of the chest demonstrating the spiculated right apical lesion (arrow) with size and characteristics similar to the previously diagnosed small-cell lung cancer.

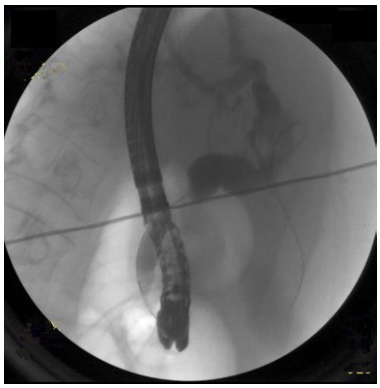

Figure 3 Endoscopic retrograde cholangiopancreatography showing dilated ducts.

ductal dilatation and multiple hypo-attenuated lesions throughout the pancreas (arrowheads), the largest noted at the pancreatic head measuring 1.7 cm × 1.6 cm (arrow). With suspicion of metastatic disease, an extensive evaluation [whole body CT scan, magnetic resonance imaging brain and a bone scan] was ordered. All these were unremarkable except for the spiculated mass in the right lung apex on chest CT (Figure 2). This was present on prior imaging and represented the previously diagnosed small-cell lung cancer (unchanged size and characteristics).

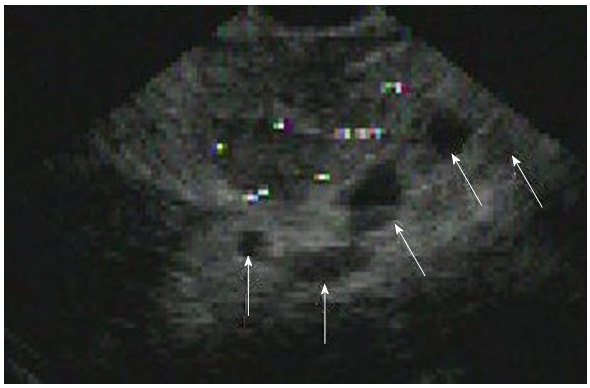

Figure 4 Endoscopic ultrasound image depicting multiple hypo-echoic lesions throughout the pancreas (arrows).

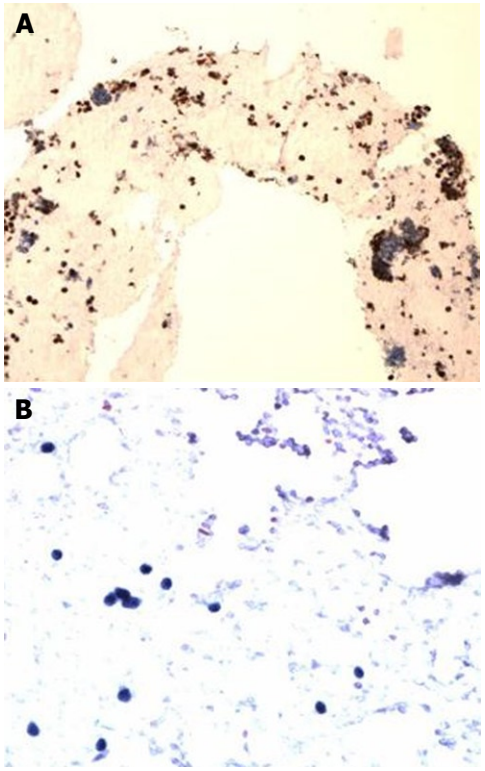

Figure 5 Fine needle aspiration cytology of the pancreas showing (A) quick stain of pancreatic mass showing small round blue cells, resembling small cell tumor, and (B) cell block of the pancreatic tissue with tumor cells positive for TTF-1 and chromogranin, indicating the origin of the tumor (lung).

Subsequently, endoscopic retrograde cholangiopancreatography (ERCP) was performed to evaluate the dilated hepatic ducts (Figure 3) and showed a biliary stricture. A sphincterotomy was performed followed by placement of a biliary stent (10 French by 9 cm) with good drainage. Endoscopic ultrasound (EUS) (Figure 4) with fine needle aspiration of the lesion in the pancreatic head (arrows) was performed and was consistent with small cell carcinoma (Figure 5A and B). The patient eventually decided to receive palliative care and was discharged home with hospice care.

DISCUSSION

A few years ago, the diagnosis of pancreatic lesions was not feasible without subjecting patients to invasive surgical procedures. Nowadays, EUS-assisted fine-needle aspiration cytology is a safe, low risk and minimally invasive method for diagnosing non-primary pancreatic neoplasms[6], which played a key role in the diagnosis of our case.

It is believed that acute pancreatitis and obstructive jaundice in biliary malignancies results from infiltration of the metastatic tumor into the pancreatic ducts. In such instances, ERCP with stent insertion can be a plausible palliative therapy for biliary drainage[7]. It resulted in dramatic resolution of our patient's obstructive jaundice. Abdominal pain subsided gradually as the pancreatic inflammation resolved. Generally, the treatment for tumor-induced acute pancreatitis and obstructive jaundice is initially supportive followed by aggressive chemotherapy or surgery. If the patient can tolerate the insertion of an endoscopic stent, then this is performed in addition to chemotherapy and surgery. This approach offers a safe and effective treatment modality for such patients.

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CASE REPORT

Acute inflammation occurring in gastric aberrant pancreas followed up by endoscopic ultrasonography

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Abstract

We describe a case of gastric aberrant pancreas with acute pancreatitis followed up with subsequent endoscopic ultrasound. A 20-year-old woman known to have aberrant pancreas in the stomach was admitted to our hospital because of severe epigastralgia. Laboratory tests showed slight C reactive protein elevation without hyperamylasemia. Esophagogastroduodenoscopy revealed a swollen submucosal lesion (SML) to a greater degree compared with the previous findings. Subsequent endoscopic ultrasonography (EUS) revealed a swollen lesion of 35 mm in diameter. The internal echo-pattern was more hypoechoic than in the previous EUS. The border between the fourth layer (muscularis propria) and the SML was unclear. The anechoic lumen in the mass, considered as the ductal lumen, was dilated. Based on these results, we diagnosed the patient as having acute inflammation, resembling pancreatitis, in the aberrant pancreas.

Key words: Aberrant pancreas; Acute pancreatitis; Endoscopic ultrasonography; Endoscopic ultrasonography- fine needle aspiration; Gastric submucosal lesion

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INTRODUCTION

Aberrant pancreas is defined as pancreatic tissue that lacks anatomic and vascular continuity with the main body of the pancreas. Aberrant pancreas is frequently seen in the stomach. Most patients with gastric aberrant pancreas are asymptomatic. They rarely present with clinical symptoms, such as abdominal pain and bleeding[1,2]. A few cases of aberrant pancreas complicated with acute inflammation like that of pancreatitis have been reported, and they are treated surgically when diagnosed with submucosal lesion (SML) of the stomach with symptoms, for which surgical pathology reveals

pancreatitis with aberrant pancreas[3-5]. We experienced a patient with acute inflammation occurring in the gastric aberrant pancreas, who was followed up by endoscopic ultrasonography (EUS) before and after the diagnosis. No report in the literature has described a similar case, although EUS images of aberrant pancreas have been presented[6]. Consequently, our case is extremely valuable from the perspective of diagnostic imaging for acute inflammation of gastrointestinal aberrant pancreas.

CASE REPORT

A 20-year-old woman with no remarkable medical history presented with epigastralgia that had continued for 3 d. Esophagogastroduodenoscopy (EGD) revealed an SML in the antrum of the stomach, but the cause of the pain was not identified. To clarify the SML pathogenesis, EUS was subsequently performed, revealing a mass located in the third layer (submucosa) with a diameter of 20 mm. The internal echo pattern was slightly more hypoechoic than the normal echo level of the third layer. It contained an anechoic lumen in the mass, which was regarded as the duct. We made a diagnosis of the aberrant pancreas of the stomach based on EGD (Figure 1A) and EUS (Figure 1B) findings. After initial examination, she had been followed up once a year using EUS to observe the changes of the SML. Four years later, she was admitted to our hospital because of severe epigastralgia.

Laboratory tests revealed that white blood cells (WBC) were 6600/μL (normal range: 3000-9800/μL); amylase (AMY), 170 IU/L (normal range, 70-240 IU/L); and C reactive protein, 2.0 mg/dL (under 0.3 mg/dL). Percutaneous ultrasound revealed an irregular large hypoechoic mass in the gastric wall with an anechoic area. The pancreas was normal. We thought that the severe epigastralgia might imply some sort of inflammation in the SML. Therefore, we performed EGD and it revealed a more swollen SML compared with the previous EGD (Figure 2). On subsequent EUS, the lesion was more swollen, with a diameter of 35 mm, and the internal echo-pattern was more hypoechoic than in the previous EUS. The border between the fourth layer (muscularis propria) and the SML was unclear (Figure 3). Based on the results of these examinations, we diagnosed the patient as having acute inflammation like pancreatitis in the aberrant pancreas.

Treatment was given following the diagnosis of acute pancreatitis. A protease inhibitor, gabexate mesylate (300 mg/d), was administrated for three days. Two months later, EUS was performed again to observe the status, which revealed that the size of SML decreased from 35 mm to 25 mm in diameter, and the internal echo pattern had improved. To establish a definite diagnosis of SML, we performed EUS-guided fine needle aspiration biopsy (EUS-FNA). The pathological examination showed ductal epithelial cells and acinar cells (Figure 4), and the SML was definitely diagnosed as an aberrant pancreas. This case was followed up without surgical operation.

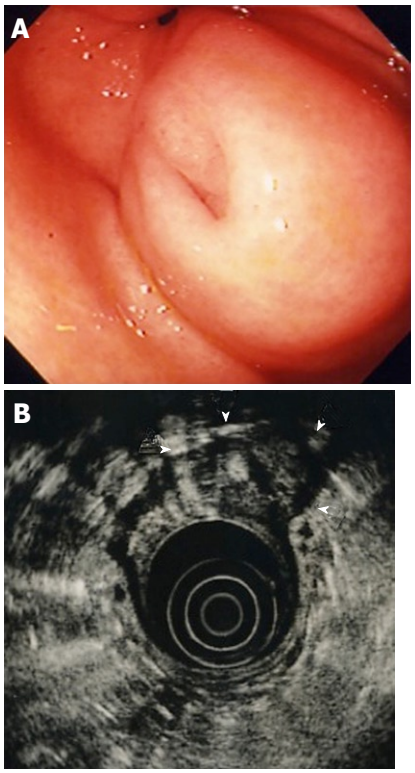

Figure 1 Esophagogastroduodenoscopic and endoscopic ultrasonographic images of submucosal lesion at the first examination. A: Esophagogastroduodenoscopy. Submucosal lesion was visible in the antrum of the stomach; B: Endoscopic ultrasonography. Lesion (arrow heads) located in the third layer (submucosa) with a diameter of 20 mm, slightly hypoechoic internal echo, and anechoic lumen, regarded as the duct.

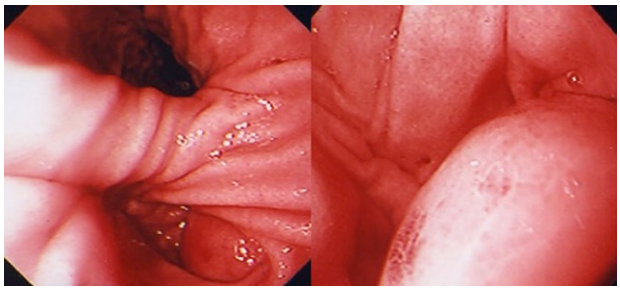

Figure 2 Esophagogastroduodenoscopy after inflammation. Esophagogastroduodenoscopy (EGD) revealed a more swollen submucosal lesion compared with the previous EGD.

DISCUSSION

Aberrant pancreas is a congenital anomaly found in the gastrointestinal tract and adjacent structures in 0.55%-14% of autopsy series; approximately 70% of all such tissues are found in the stomach, duodenum, and jejunum[3,7,8]. Patients with aberrant pancreas are usually asymptomatic. Therefore, the lesion is often found incidentally during clinical investigation for other gastroduodenal diseases[9]. However, aberrant pancreas sometimes produces symptoms associated with pancreatitis, cyst formation, ulceration, bleeding, obstructive jaundice, and gastric outlet obstruction[10].

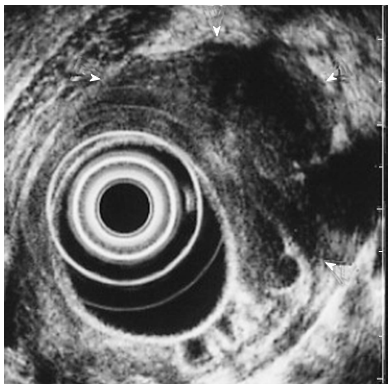

Figure 3 Endoscopic ultrasonographic image after inflammation. On endoscopic ultrasonography (EUS), the lesion was more swollen, with a diameter of 35 mm. The internal echo-pattern was more hypoechoic than in the previous EUS (arrow heads).

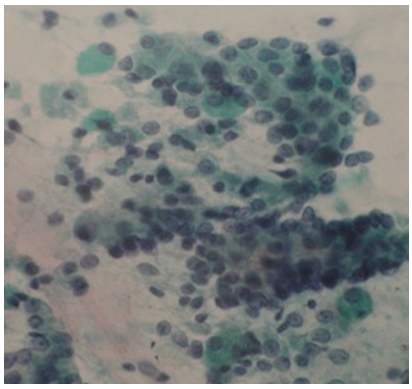

Figure 4 Pathological findings of submucosal lesion. Pathologic examination showed ductal epithelial cells and acinar cells.

Acute pancreatitis occurring in the gastrointestinal aberrant pancreas is rare. In the relevant literature, a major symptom of this pathosis was described as abdominal pain. Almost all cases show slight elevation of serum amylase. Aberrant pancreas can be classified into three histological types. Type Ⅰ designates a typical pancreatic tissue with acini, duct, and islet cells resembling those of a normal pancreas. Type Ⅱ aberrant pancreatic tissue comprises a pancreatic tissue with numerous acini and a few ducts lacking islet cells. Finally, type Ⅲ in which only excretory ducts were observed[11]. Therefore, aberrant pancreas (especially types Ⅰ and Ⅱ) might demonstrate the full range of pancreatic pathologies including pancreatitis (acute and chronic) as well as benign and malignant neoplastic transformations[12,13]. To date, some reports have described acute or chronic pancreatitis occurring in the aberrant pancreas[3-5,13,14]. It remains controversial whether acute or chronic inflammatory changes in aberrant pancreas are induced by similar pathogenesis to that of pancreatitis in anatomical pancreas. In a reported case of chronic pancreatitis derived from Heinrich type Ⅱ (no drainage duct microscopically) aberrant pancreas, aberrant pancreatic tissue might be more susceptible to pancreatitis because of the lack of drainage ducts in Heinrich type Ⅱ[13]. Such a pathosis as in this case will also apply to the etiology of acute pancreatitis in aberrant pancreas. However, it was reported that in patients with chronic alcoholic pancreatitis associated with aberrant pancreas, microscopic examination of the aberrant pancreas showed no changes that were suggestive of chronic pancreatitis, despite severe chronic pancreatitis in the main pancreas[15]. Consequently, these reports suggest that the acute or chronic pancreatitis derived from aberrant pancreas might occur because of some sort of ductal obstruction, but not from direct injury of acini caused by heavy alcohol consumption. In the case described herein, the pathological findings obtained by EUS-FNA showed ductal epithelial cells and acinar cells, indicating Heinrich type I. The patient reported no alcohol abuse. Therefore, we assume that the pathogenesis of acute pancreatitis of the aberrant pancreas might be obstruction of ductal system in the ectopic tissue from any cause.

It is notable in our case that the inflammation of aberrant pancreas was followed up by EUS. No report in the literature describes such a case and provides images of acute pancreatitis derived from aberrant pancreas using EUS. The image of acute pancreatitis in aberrant pancreas is similar to acute inflammation of anatomic pancreas: swelling with heterogeneous parenchymal echo pattern. These images do not resemble those of a tumor with necrosis such as gastrointestinal stromal tumor, or abscess/phlegmonous gastritis with SML[16]. We believe that images such as those related to our case were not observed on EUS except for acute inflammation of aberrant pancreas. Therefore, we should be aware that a gastric aberrant pancreas can cause acute pancreatitis and must be suspected in patients with atypical abdominal pain and SMT in the stomach. EUS is strongly recommended for the definite diagnosis in such a case.

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CASE REPORT

A case of chronic pancreatitis in which endoscopic ultrasonography was effective in the diagnosis of a pseudoaneurysm

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Abstract

Endoscopic ultrasonography (EUS) was performed on a patient being treated for chronic pancreatitis because a submucosal tumor was observed in the stomach during gastrointestinal endoscopy. As internal pulsatile blood flow on Doppler was present, the diagnosis of an aneurysm was made. The pseudoaneurysm of the left gastric artery was embolized with histoacryl and lipiodol and the splenic artery was embolized with coils at the location of the pseudoaneurysm to prevent hemorrhage. Follow up EUS confirmed the cessation of blood flow from the pseudoaneurysm. Clinicians encountering a gastric submucosal tumor-like protrusion in a patient with chronic pancreatitis should use EUS to investigate the possibility of a pseudoaneurysm, which must be treated as quickly as possible once identified.

INTRODUCTION

Pseudoaneurysms are a known complication of chronic pancreatitis. Untreated, pseudoaneurysms may rupture, and can be fatal.

We herein describe a patient with chronic pancreatitis who was diagnosed with a pseudoaneurysm of the left gastric artery while undergoing endoscopic ultrasonography (EUS) for a gastric submucosal tumor-like protrusion.

CASE REPORT

The patient, a 39-year-old male, presented with the primary complaints of chest tightness and upper abdominal pain. Previously, the patient had been repeatedly admit-

ted and discharged for alcoholic pancreatitis. An approximately 4 cm, left mediastinal, cystic lesion continuing from the tail of the pancreas was seen on multidetector row computed tomography (MDCT) at the time of presentation. An area of high density was observed within the cyst, and a severely atrophied pancreas with a calcified body was observed (Figure 1). As a pseudocyst complicating an acute exacerbation of chronic pancreatitis and hemorrhage in the pseudocyst was suspected, it was suggested that the patient be admitted for a detailed examination. However, the patient, refused to be admitted for a detailed examination as recommended, and returned home. Later, when his symptoms progressively worsened and his stool had been black for 1 wk, he was rushed to the hospital.

At the time of admission, his blood pressure was 105/60 mmHg, his pulse was regular at 90 bpm, and his temperature was 37.2 °C. The patient's abdomen was soft, flat, and slightly distended, with mild tenderness in the upper abdomen. The laboratory findings were as follows: marked anemia with hemoglobin of 7.2 g/dL, amylase of 262 IU/L, mildly elevated pancreatic enzymes with lipase of 109 IU/L, and an inflammatory response with C-reactive protein of 4.76 mg/dL. Following admission, 4 units of packed red blood cells were transfused to treat anemia. Endoscopic retrograde pancreatography (ERCP) was performed to further investigate and treat the pseudocyst. Pancreatography revealed stenosis of the principal pancreatic duct at the head, dilation of the duct at the tail, and a communication between the tail duct and the pseudocyst (Figure 2). Therefore, the pancreatic duct was stented (stent size, 7 Fr, 7 cm). Although no substantial bleeding in the upper gastrointestinal tract was seen during ERCP, upper gastrointestinal endoscopy was performed to investigate the marked anemia which was present on admission. Endoscopy revealed a 2 cm protrusion resembling a submucosal tumor in the lesser curvature of the middle of the body of the stomach (Figure 3). EUS using the GF-UE260-AL5 (Olympus, Tokyo, Japan) and Prosound α10 (Aloka, Tokyo, Japan) was performed for diagnosis. On EUS, a 1 cm submucosal anechoic region whose entire periphery was hypoechoic was seen. The pulsating anechoic mass with Doppler signal enhancement identified in the gastric submucosa was diagnosed as an aneurysm with hematomas around the periphery (Figure 4A). Angiography proceeded, and a 1 cm pseudoaneurysm of the left gastric artery and a large pseudoaneurysm of the splenic artery measuring 2 mm in diameter were detected. Hemorrhage was prevented with transluminal embolization using lipiodol and histoacryl because a small aneurysm was observed in the left gastric artery upon angiography. This was embolized with coils as a pseudoaneurysm measuring 2 mm was further observed in the splenic artery (Figure 5).

Cessation of blood flow to the pseudoaneurysm was confirmed on EUS performed 1 wk later (Figure 4B). Since there was no subsequent bleeding, follow-up MDCT was performed 1 mo later. The left mediastinal pseudocyst had shrunk markedly.

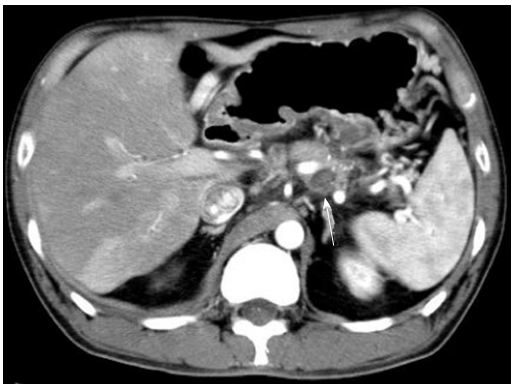

Figure 1 Abdominal computed tomographic findings. A severely atrophied pancreas with a calcified body was noted. The pseudocyst (arrow) ranged from the back of the pancreas to the left mediastinum and was adjacent to the splenic artery.

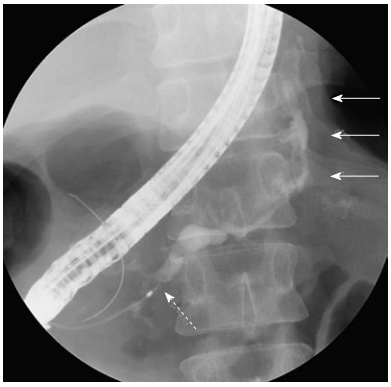

Figure 2 Endoscopic retrograde pancreatography findings. A: Endoscopic retrograde pancreatography showed stenosis of the principal pancreatic duct at the pancreatic head (dotted arrow) and a dilated tail duct communicating with the left mediastinal pseudocyst (solid arrows).

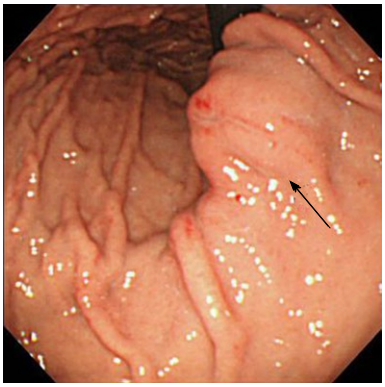

Figure 3 Upper gastrointestinal endoscopy findings. Upper gastrointestinal endoscopy showed a 2 cm, submucosal tumor-like protrusion with a red, eroded upper region located in the lesser curvature of the middle of the body of the stomach (arrow).

DISCUSSION

Hemorrhage in the pseudocyst was seen on MDCT at the time of presentation and ERCP performed after ad-

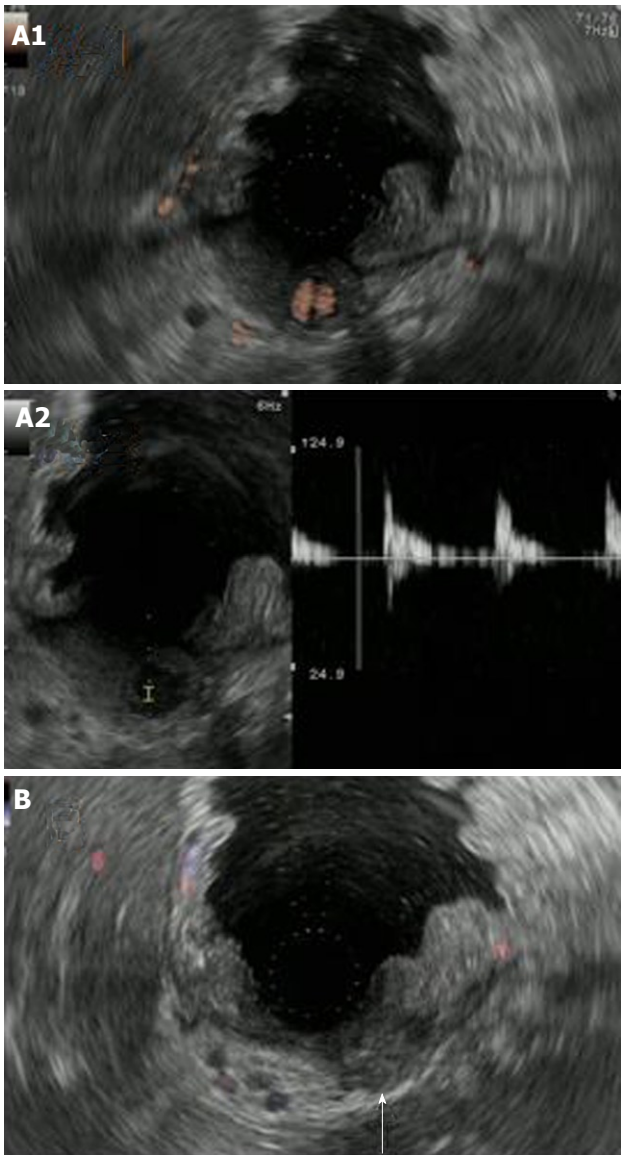

Figure 4 Endoscopic ultrasonography findings. A1: Endoscopic ultrasonography showed an anechoic region whose entire periphery was hypoechoic beneath the gastric mucosa. Power Doppler showed blood flow in the anechoic region. Upper gastrointestinal endoscopy showed a 2 cm, submucosal tumor-like protrusion with a red, eroded upper region located in the lesser curvature of middle of the body of the stomach (arrow); A2: Pulsed wave Doppler showed pulsatile blood flow in the anechoic region. This finding led to the diagnosis of an aneurysm; B: The cessation of blood flow to the pseudoaneurysm was confirmed with endoscopic ultrasonography which was performed 1 wk after treatment (arrow).

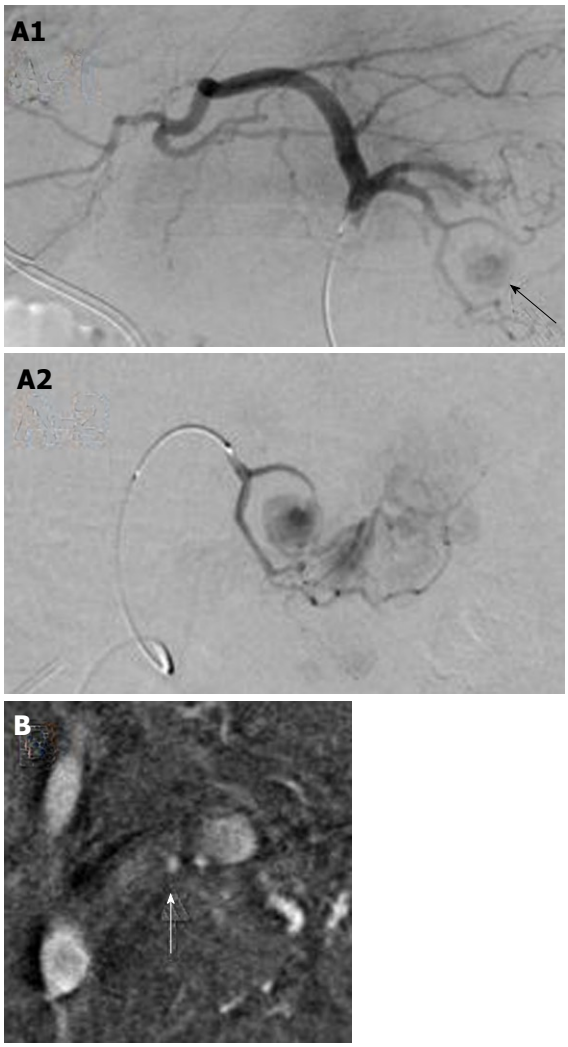

Figure 5 Angiography findings. A1: The pseudoaneurysm of the left gastric artery was diagnosed on angiography (arrow). The left hepatic artery diverged from the left gastric artery; A2: The microcatheter was advanced in the region of the pseudoaneurysm, and the pseudoaneurysm was embolized with histoacryl and lipiodol; B: A small pseudoaneurysm was observed in the splenic artery (arrow), and the splenic artery was embolized by coils.

mission revealed a communication between the tail duct and the pseudocyst. It is thought that the splenic pseudoaneurysm was bleeding into the pseudocyst because the splenic artery was adjacent to the pseudocyst on MDCT. No bleeding from Vater's papilla was observed when carrying out ERCP, but it was presumed that hemosuccus was the cause of this bleeding as the patient had black stool in the week preceding admission and was markedly anemic upon admission. The resulting progress of anemia triggered the discovery of a pseudoaneurysm in the left gastric artery which was on the verge of rupturing.

Although a pseudoaneurysm complicating chronic pancreatitis occurs relatively infrequently and affects only 6% to 9% of patients[1], 40% to 60% of ruptured pseudoaneurysms result in a fatal outcome[2]. Pseudoaneurysms are primarily attributed to the digestion and lysis of the arterial wall near the pancreas by errant activated pancreatic enzymes[3]. The splenic artery is the most commonly affected site. Pseudoaneurysms also frequently form in the gastroduodenal, pancreaticoduodenal, and hepatic arteries, but rarely in the left gastric artery[4,5]. Aneurysms of the left gastric artery mimicking a gastric submucosal tumor are also extremely rare[2,4].

The MDCT examination performed on admission may have missed the aneurysm because the lesion was small or because collateral circulation attributable to pancreatitis-induced pancreatic arteriovenous occlusion resulted in the imaging of many winding blood vessels which, in turn, complicated the identification and diagnosis of the aneurysm. EUS, which can show the gastric

Table 1 Cases of pseudoaneurysm diagnosed on endoscopic ultrasonography

Reported by	Aneurysm site	SMT-like lesion site	Underlying disease	Symptoms	Treatment
Mosler *et al*[7]	Splenic artery	Posterior wall of cardiac part	None	Anemia	
Chaya *et al*[8]	Splenic artery	Greater curvature of fundus	Arteriosclerosis	Gastrointestinal bleeding	Surgery
Falodia *et al*[2]	Left gastric artery	Posterior wall of cardiac part	Chronic pancreatitis	Gastrointestinal bleeding	Embolization
Jani *et al*[9]	Left gastric artery	Posterior wall of body of stomach	Alcoholic cirrhosis	Gastrointestinal bleeding	Embolization
Higuchi *et al*[10]	Splenic artery × 4	Posterior wall of fundus	None	None	-
Present case 2011	Left gastric artery	Lesser curvature of middle of body	Chronic pancreatitis	Anemia	Embolization

SMT: Submucosal tumor; -: No description.

wall in fine detail, is an excellent tool for diagnosing gastric submucosal lesions[6]. The added Doppler functionality of the particular EUS device used in the present case made the device better suited than MDCT for diagnosing and following small aneurysms resembling submucosal tumors.

Recently, higher rates of detection have been related to the increased frequency of imaging studies such as EUS[5]. A search of the literature revealed only this case and 8 other cases of submucosal tumor-like protrusions diagnosed as pseudoaneurysms on EUS[2,7-10]. The responsible vessel was the splenic artery in 6 cases and the left gastric artery in 3. The submucosal tumor-like lesion was often located in the fundus or cardiac area (7 of 9) and posterior wall (7 of 9). Two of the patients had chronic pancreatitis, one had alcoholic cirrhosis, one had arteriosclerosis, and five had no underlying disease. The lesions were coincidentally discovered during upper gastrointestinal endoscopic screening in four of these patients. Three of the patients had gastrointestinal bleeding that was treatable with either embolization or surgery (Table 1).

The danger of re-bleeding after embolization increases if pancreatitis continues even following treatment, but we believe that we were able to successfully control bleeding by avoiding stent implantation in the pancreatic duct and by avoiding bleeding. A pseudoaneurysm should be suspected when a gastric submucosal tumor-like protrusion is seen in a patient with chronic pancreatitis. We recommend that EUS be carried out, and if a pseudoaneurysm is diagnosed, then interventional radiology should be performed as soon as possible. In addition, the successful control of pancreatitis was believed to be the key to successful bleeding control.

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January 20-21, 2012
American Gastroenterological Association Clinical Congress of Gastroenterology and Hepatology
Miami Beach, FL 33141, United States

February 2-4, 2012
14th Dusseldorf International Endoscopy Symposium 2012
Dusseldorf, Germany

February 24-27, 2012
Canadian Digestive Diseases Week 2012
Montreal, Canada

March 1-3, 2012
International Conference on Nutrition and Growth 2012
Paris, France

March 7-10, 2012
Society of American Gastrointestinal and Endoscopic Surgeons Annual Meeting
San Diego, CA 92121, United States

March 12-14, 2012
World Congress on Gastroenterology and Urology
Omaha, NE 68197, United States

March 30-April 2, 2012
Mayo Clinic Gastroenterology and Hepatology
San Antonio, TX 78249, United States

March 31-April 1, 2012
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April 8-10, 2012
9th International Symposium on Functional GI Disorders
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April 15-17, 2012
European Multidisciplinary Colorectal Cancer Congress 2012
Prague, Czech

April 19-21, 2012
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New Orleans, LA 70166, United States

April 20-22, 2012
Diffuse Small Bowel and Liver Diseases
Melbourne, Australia

April 22-24, 2012
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Madrid, Spain

April 28, 2012
Issues in Pediatric Oncology
Kiev, Ukraine

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9th Congress of The Jordanian Society of Gastroenterology
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May 7-10, 2012
Digestive Diseases Week
Chicago, IL 60601, United States

May 17-21, 2012
2012 ASCRS Annual Meeting-American Society of Colon and Rectal Surgeons
Hollywood, FL 1300, United States

May 18-23, 2012
SGNA: Society of Gastroenterology Nurses and Associates Annual Course
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May 19-22, 2012
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Pancreatic Cancer: Progress and Challenges
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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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