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Colonoscopy revealed a slightly reddish subpedunculated polyp, about 12 mm in diameter, in the lower rectum. The surface of the polyp was covered with whitish exudate, which suggested inflammatory change.

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EDITORIAL

Endoscopic approach to pancreatic pseudocysts: An American perspective

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Abstract

Pancreatic pseudocysts, abscesses, and walled-off pancreatic necrosis are types of pancreatic fluid collections that arise as a consequence of pancreatic injury. Pain, early satiety, biliary obstruction, and infection are all indications for drainage. Percutaneous-radiologic drainage, surgical drainage, and endoscopic drainage are the three traditional approaches to the drainage of pancreatic pseudocysts. The endoscopic approach to pancreatic pseudocysts has evolved over the past thirty years and endoscopists are often capable of draining these collections. In experienced centers endoscopic ultrasound-guided endoscopic drainage avoids complications related to percutaneous drainage and is less invasive than surgery.

Key words: Pancreatic fluid collections; Pseudocyst; Endoscopic drainage

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INTRODUCTION

Acute pancreatitis is an acute inflammatory process of the pancreas with variable involvement of surrounding tissues or remote organ systems[1]. It is the second most common inpatient principal gastrointestinal diagnosis in the United States[2]. More than 80% of the cases of acute pancreatitis are due to gallstones or alcohol consumption while the remaining 20% is due to viruses, drugs, trauma, metabolic and genetic abnormalities and complications associated with Endoscopic Retrograde Cholangeopancreatography (ERCP). Complications of pancreatitis include renal failure, coagulopathy, hypocalcemia, splenic vein thrombosis, gastrointestinal hemorrhage, and the development of pancreatic fluid collections.

BODY

Pancreatic pseudocysts, abscesses, and walled-off pancreatic necrosis are types of pancreatic fluid collections that arise as a consequence of pancreatic injury. The basis of the pancreatic injury is disruption of the pancreatic duct or side branches that result in the formation of a collection of fluid with or without solid debris[3]. Pain, early satiety, biliary obstruction, and infection are all indications for drainage. Percutaneous-radiologic drainage, surgical drainage, and endoscopic drainage are the three accepted approaches to the drainage of pancreatic pseudocysts. The therapeutic approach to pancreatic pseu-

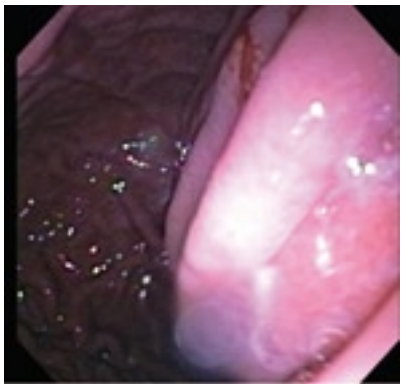

Figure 1 Visible bulge in a patient with a pancreatic pseudocyst.

docysts has evolved over the past thirty years. What once was treated with a surgical or percutaneous approach is now being managed via endoscopy.

Radiologic guidance allows placement of a drainage pigtail catheter into the pancreatic pseudocyst allowing subsequent drainage. The catheter is connected to an external collection system and fluid is collected over several weeks. In order to monitor resolution of the pseudocyst, contrast is injected periodically into the cyst cavity and repeat imaging is performed. The percutaneous drainage approach is useful in high risk patients who would not tolerate the endoscopic or surgical approach because of confounding co-morbidities. However this technique makes the patient more prone to infection, produces significant patient discomfort, and might require multiple catheter exchanges because of catheter clogging. In those patients who have failed the percutaneous approach, a surgical option would be appropriate. In this setting, a fistula is surgically created between the pseudocyst and the stomach or the small bowel, allowing for complete drainage. Many studies have been performed that have shown a significantly higher mortality rate associated with surgical therapy compared with other approaches[4].

In the past thirty years, the endoscopic approach to pancreatic fluid collections has evolved greatly. The armamentarium of the endoscopist has allowed potentially successful drainage of pseudocysts and even walled-off pancreatic necrosis. The basis of the pancreatic injury is disruption of the pancreatic duct or side branches that result in the formation of a collection of fluid with or without solid debris. One of the first endosopic approaches to pancreatic pseudocysts was reported by Rogers where a woman with a history of alcohol abuse and pseudocysts due to recurrent pancreatitis presented with epigastric abdominal pain. An upper gastrointestinal series revealed a 10 cm pressure defect in the posterior aspect of the stomach which was confirmed endoscopically. An aspirating device constructed from the shaft of a 21 gauge needle and Teflon tubing was advanced through the biopsy channel and used to aspirate fluid from the aforementioned cyst. It is likely that this pseudocyst had communication with the pancreatic duct as repeat imaging three days later demonstrated that the cyst had refilled[5].

Kozarek *et al* in 1985 reported the first series of endoscopic drainage of pancreatic pseudocysts. They described endoscopic cystostomy in four high risk patients in whom surgery had been either unsuccessful or was felt to be contraindicated. An endoscopically visible bulge was identified in each case and the cystotomy was completed with a modified straight wire sphincterotome that was inserted through the stomach or the duodenum and into the pseudocyst[6]. Over the past twenty years the endoscopic approach to pseudocysts has evolved to include; transpapillary drainage, transmural drainage with or without endosonograpic guidance, or combined transmural and transpapillary drainage. Endoscopic pseudocyst drainage is safe when there are no associated pseudoaneurysms, gastric or duodenal varices demonstrated on noninvasive imaging modalities and the intended site of cyst wall puncture is within one cm of the bowel lumen. The approach that the endoscopist will employ for endoscopic drainage is based on the anatomical relationship of the collection to the stomach or duodenum, the presence of ductal communication, and the size of the collection[7].

Since Kozarek demonstrated pseudocyst drainage endoscopically more than twenty years ago, the conventional endoscopic approach has been customized. Transluminal drainage may be accomplished *via* a transgastric, transduodenal, or even transesophageal route[8]. Studies performed to determine whether the transduodenal or transgastric approach had better long-term results, have not shown any superiority for either approach[9,10]. Conventional endoscopic drainage is feasible when a visible bulge is seen in the stomach or the duodenal wall (Figure 1). With a Seldinger technique, an aspirating needle is passed transluminally into the pseudocyst collection, and fluid is aspirated to confirm entrance into the pseudocyst. Once confirmation has been made that the collection is a pseudocyst, contrast medium is injected to confirm needle localization within the pseudocyst cavity. A 0.035 guide wire with a hydrophilic tip is inserted and coiled into the collection as the needle is removed. A cannula is now passed over the wire to perform an initial dilatation. If there is resistance due to a thick wall then needle-knife electrocautery can be performed in a forward pressure maneuver over the wire[11]. Once a tract has been made a biliary dilating balloon catheter can be used to further dilate the tract. Simultaneous endoscopic and fluoroscopic imaging confirms the position of the balloon and waist obliteration during balloon inflation. The balloon is removed and two double pig-tail stents are typically placed over the guide wire (Figure 2). Most authorities feel that the use of double pig tail stents will reduce stent migration and allow for expeditious drainage[12].

Endoscopic drainage performed without a visible endoluminal bulge carries significant risk of bleeding and perforation. In a series reported by Sahel *et al*[13] and Cremer *et al*[10] perforation occurred in 2 of 20 patients without visible endoluminal bulge and bleeding occurred in 2 of 33 patients who had no endoluminal bulge.

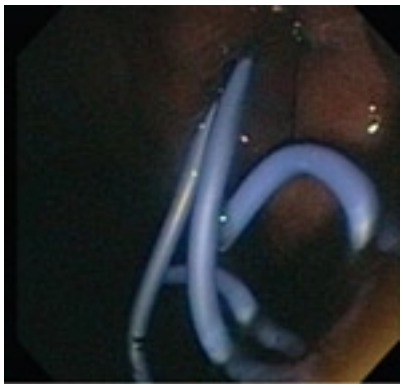

Figure 2 Placement of two 7FR pigtail stents.

Figure 3 Endosonographic view of pancreatic pseudocyst.

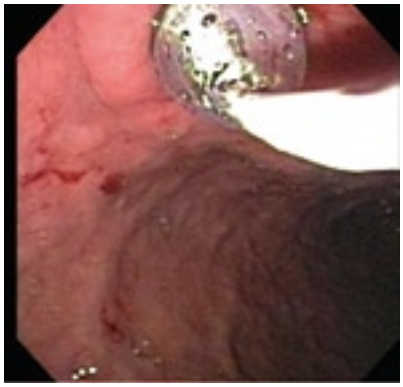

Figure 4 Balloon dilatation after cautery.

Grimm *et al*[14] reported a case of pseudocyst puncture under direct endosonographic guidance using an electronic oblique scanning echoendoscope in a patient without endoscopic evidence of extramural pseudocyst bulging. Endoscopicultrasound (EUS) can be used to confirm that the pseudocyst is adjacent to the stomach or duodenum with the distance measuring less than one cm and to exclude associated pseudoaneurysms (Figure 3). Until recently the echoendoscope was replaced, after the enterostomy site was marked, with a duodenoscope and the enterostomy was performed. Transmural drainage of pancreatic fluid collections performed entirely under EUS guidance using Doppler-equipped therapeutic channel echoendoscopes was first described by Giovannini *et al*[15]. Recently a "one-step" technique for drainage of pancreatic fluid collections using the Needle-Wire Oasis System has been described. The first step of this procedure is to puncture the pseudocyst using the needle-wire by applying electrocautery. When the needle wire is inside the pseudocyst, the internal rigid part of the needle-wire is removed and the guide wire is coiled into the pseudocyst. The second step is to dilate the tract using a dilator catheter (Figure 4) and finally deliver the stent using a pusher, similar to the technique adopted for biliary stenting[16].

Studies have been performed to evaluate which is the best modality to drain pancreatic pseudocysts; the conventional endoscopic approach or endoscopic ultrasound guided. Kaheleh *et al* prospectively compared their experience in EUS-guided cystenterostomy with that in contemporaneous group of patients with pseudocysts drained using conventional transmural drainage. A total of 99 patients underwent endoscopic management of pancreatic pseudocysts. Patients with bulging lesions without obvious portal hypertension underwent conventional endoscopic drainage; all others underwent endoscopic ultrasound drainage. Patients were followed with cross sectional imaging during clinical visits and results were compared at 1 and 6 mo post procedure. Forty-six underwent endoscopic ultrasound drainage and the remaining 53 had the conventional drainage performed. There were no significant differences between the two groups regarding either short-term or long-term success. Complications occurred in 19% of the endoscopic ultrasound group *vs* 18% of the conventional drainage group, and consisted of bleeding in three cases, infected collection in eight, stent migration in three, and pneumoperitoneum in five[17]. Varadarajulu *et al* performed a randomized study and compared the rate of technical success between EUS and Esophagogastroduodenoscopy (EGD) for transmural drainage of pancreatic pseudocysts. Those included in the study were patients with a history of pancreatitis and symptomatic pancreatic pseudocysts that were greater than 4 cm in size. Technical success was defined as the ability to access and drain a pseudocyst by placement of a transmural stent. Complications were assessed at 24 h and at day 30. Treatment success was defined as the complete resolution or decrease in size of the pseudocysts to less than 2 cm on CT, in association with clinical resolution of symptoms at 6 wk follow-up. Thirty patients were randomized to undergo pseudocyst drainage; fifteen were randomized to EUS and the remaining fifteen to the EGD approach. Of the fifteen under the EUS approach, 14 underwent successful drainage while the procedure was technically successful in only five of fifteen randomized to EGD. Reasons for technical failure in these ten patients were: the absence of luminal compression in nine and active bleeding after attempted puncture of the pseudocyst in one patient. All ten patients who failed drainage by EGD underwent successful drainage of pseudocyst on crossover to EUS[18]. More studies are needed in this comparison. However, it seems that EUS, given its excellent safety profile, should be considered first-line treatment modality for endoscopic drainage of pancreatic pseudocysts.

The transpapillary approach is preferable when com-

munication is demonstrated between the pancreatic ductal system and the pseudocyst. A pancreatogram is obtained during ERCP and if the pseudocyst fills with contrast medium, then communication with the main pancreatic ductal system is confirmed. Visualization of the main pancreatic duct beyond the site of communication between the duct and the pseudocyst is not always seen, either because of duct disconnection or the preferential flow of contrast medium into the pseudocyst cavity. Pancreatic sphincterotomy is performed as it will facilitate the introduction of stents and/or dilating devices and may promote transpapillary flow around the stent. Using a hydrophilic guidewire, the leak should be traversed so that patency of the main pancreatic duct is achieved. Stent sizes are dependent on the pancreatic duct diameter but are usually 7Fr, and continuity of the main pancreatic duct should be accomplished when placing the stent across the ductal leak[19,20]. The use of both transpapillary and transmural drainage should be considered in very large pseudocysts (> 6 cm) or cases in which there is a pancreatic ductal abnormality.

CONCLUSION

The endoscopic approach to pancreatic pseudocysts has evolved over the past thirty years. What once was only in the domain of the surgeon or the interventional radiologist is now being treated endoscopically in specialized centers. Fluid collections with a mature wall within 1 cm of the gastrointestinal lumen should be considered for endoscopic drainage. Studies comparing the surgical, percutaneous, and endoscopic pseudocyst drainage procedures are lacking.

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TOPIC HIGHLIGHT

Sedation-risk-free colonoscopy for minimizing the burden of colorectal cancer screening

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Abstract

Unsedated colonoscopy is available worldwide, but is not a routine option in the United States (US). We conducted a literature review supplemented by our experience and expert commentaries to provide data to support the use of unsedated colonoscopy for colorectal cancer screening. Medline data from 1966 to 2009 were searched to identify relevant articles on the subject. Data were summarized and co-authors provided critiques as well as accounts of unsedated colonoscopy for screening and surveillance. Diagnostic colonoscopy was initially developed as an unsedated procedure. Procedure-related discomfort led to wide adoption of sedation in the US, although unsedated colonoscopy remains the usual practice elsewhere. The increased use of colonoscopy for colorectal cancer screening in healthy, asymptomatic individuals suggests a reassessment of the burden of sedation in colonoscopy for screening is appropriate in the US for lowering costs and minimizing complications for patients. A water method developed to minimize discomfort has shown promise to enhance outcomes of unsedated colonoscopy. The use of scheduled, unsedated colonoscopy in the US appears to be feasible for colorectal cancer screening. Studies to assess its applicability in diverse practice settings deserve to be conducted and supported.

Key words: Unsedated colonoscopy; Sedation-risk-free colonoscopy; Colon cancer screening

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INTRODUCTION

Optical colonoscopy is a necessary follow-up step of all positive colorectal cancer screening tests and is itself one of the recommended modalities for screening. Sedation is usual practice in the United States (US)[1]. Its burden includes escort requirement, time for recovery and activity restrictions[2]. Anecdotally, to obviate these limitations, busy, knowledgeable endoscopists, chiefs of gastroenterology divisions and medicine department chairs have requested scheduled, unsedated colonoscopy for their own screening and surveillance[3], indicating that the option is not necessarily "inferior or inhumane". When informed of the details (Table 1), patients have chosen scheduled, unsedated colonoscopy because they do not need to have an escort[4,5]. Reports of effective ways of presenting various options and improved techniques for performance of unsedated colonoscopy have been published in recent years[5,6]. This new knowledge is essential for paving the way towards more widespread application of these screening options and potentially enhancing participation. The purpose of this invited review is to raise awareness of the appropriateness of unsedated colonoscopy in reducing patient burden in screening.

METHOD

Medline data from 1966 to 2009 were searched to identify relevant articles on the subject. Data were summarized and co-authors provided critiques as well as accounts of unsedated colonoscopy for screening and surveillance.

REULTS OF LITERATURE REVIEW

Flexible fiberoptic colonoscopy was developed as an unsedated procedure in the late 1960's[7]. Cecal intubation in difficult diagnostic cases for the pioneer expert colonoscopists was enhanced by sedation[8]. Sedation also improved the cecal intubation rates of less skillful colonoscopists[9]. A number of US clinicians have proposed options besides routine sedation[4-6,10-19]. Scheduled, unsedated colonoscopy is acceptable to patients who value communication with the colonoscopist, or when they lack an escort[4-6,10-19]. Nonetheless sedation remains the dominant practice[1] and for colonoscopists' efficiency and economic reasons[20] deep sedation is gaining support in the US[21].

On the other hand, unsedated colonoscopy has continued to be practiced in many parts of the world[22-40] (see Table 2). The need to minimize sedation-related complications in healthy, asymptomatic, average risk individuals undergoing screening or surveillance colonoscopy has been emphasized by authors (mostly non US) who reported new devices for enhancing the performance of unsedated colonoscopy[41-45].

Unsedated colonoscopy conveys the negative stigma that patients are deprived of medications to ensure relief and amnesia of the discomfort[46-49]. How can these options be presented to encourage their consideration by both colonoscopists and patients? We earlier proposed the term "sedation-risk-free" colonoscopy[50] for discussion. The term sedation-free colonoscopy was used to lessen the negative impact of no sedation[28,29]. It was used in describing a more tolerable examination performed with an upper endoscope in patients with low body mass index[26], to assess patient factors predictive of pain and difficulty[24] or completion[23] of colonoscopy. We advanced the term sedation-risk-free colonoscopy to emphasize its significance in minimizing the burden of sedation-related complications[50]. In a recent editorial[5], the implication has been extended to lessening the time burden[2] of screening for colorectal cancer.

Table 1 Comparison of sedated and unsedated colonoscopy

	Sedated	Unsedated
Medication risks (hypotension, hypoxia, arrhythmia)	Very, very small	None
Success rate of cecal intubation	~ 90%	80% to 90%
Purge preparation	Mandatory	Mandatory
Escort	Mandatory	Not required
Driving immediately after colonoscopy	Not allowed	Allowed
Discomfort reduced by medication	Very likely	Not applicable
Remember discomfort	No	Yes
Remember discussion during and after colonoscopy	No	Yes
Need monitoring for 15 to 60 min after colonoscopy depending on type and dosage of sedation medications used	Yes	No
May require repeat with sedation	Not applicable	If examination is incomplete

One practical approach is to present the option as an extended sigmoidoscopy[14,15,51]. Sigmoidoscopy for colorectal cancer screening is supported by evidence from case controlled studies[52], although it is not the preferred method in many countries because 40% of all colorectal neoplasia would be overlooked. A recent report of colonoscopy reducing death from left, but not right-sided colon cancer[53] suggests that sigmoidoscopy[54-56] does have a place in screening. Sigmoidoscopy is performed without sedation coverage. Extended sigmoidoscopy is performed with the aid of a colonoscope after full bowel preparation by oral purgative[15]. Without the use of medications, both extended sigmoidoscopy and unsedated colonoscopy obviate nursing cost for monitoring and recovery[4,5,15], the risk of complications[57] and patient burden[2] inherent in sedation. Presentation, however, is dramatically different. In the former, reaching colonic segments proximal to the splenic flexure is added yield after completion of screening. In the latter, not reaching the cecum is a failure to complete screening. Extended sigmoidoscopy also leaves the option to accept full colonoscopy without sedation to the patient based on tolerable abdominal discomfort[15]. Until unsedated colonoscopy sheds its

Table 2 Worldwide practice of sedation-risk-free colonoscopy

Endoscopist (location) (N)	Cecal intubation (%)	Special technique	Incomplete/difficult intubation	Predictor(s) of pain	Ref.
GI (Taiwan) (176)	97.70	Colonoscopy	Intolerance (n = 2), technical difficulty (n = 1), poor preparation (n = 1)	Female gender and the endoscopist	[22]
Surgeon (Taiwan) (109)	85.30		Previous gynecological surgery		[23]
GI (Italy) (510)	95.70	Oil, warm water *vs* air			[24]
GI (Korea) (426)	95.30		Older age, lower body mass index (BMI) and previous hysterectomy	Older age, lower BMI, hysterectomy, diarrhea, 1st time colonoscopy and anxiety	[25]
GI (Korea) (N = 244) (Low BMI n = 77)	97.7 (UE) *vs* 79.4 (C) (low BMI)	Upper endoscope (UE) *vs* Colonoscope (C)	9.3% (UE) *vs* 32.4% (C) (low BMI)	Use of C rather than UE	[26]
GI (France) (502)	78	Music	Pain, poor bowel prep		[27]
GI (Japan) (848)	99.60		Lower BMI, female, preparation status, previous hysterectomy	Lower BMI, younger age, intubation time, preparation status, previous hysterectomy	[29]
GI (Japan) (287)	96	Ultrathin *vs* pediatric or standard scope	looping in the ultrathin group, angulations or stricture in the pediatric and standard groups		[30]
GI (Saudi Arabia) (503)	67		Incomplete due to inadequate bowel prep (14.3%), due to pain (9.5%)		[31]
GI (Turkey) (120)	88			Mean pain score: 2.0 for the nonsedated and 3.8 for the sedated patients (P < 0.05).	[32]
GI (Croatia) (22)				2 of 22 patients in whom no sedation was used had oxygen saturation < 90 %	[33]
GI (Japan) (259)	95-96	Water instillation *vs* air insufflations		17.1% (water) and 33.3% (air) had abdominal pain (P < 0.001)	[34]
GI (Italy) (124)		On demand sedation (66% required sedation)		34% reported moderate or severe pain and 22% unwilling to repeat	[35]
GI (Norway) (409)	82 (90 willing to repeat)			Overall cohort: 5% very, 45% moderately, 50% not uncomfortable; 63% women *vs* 41% men, very or moderately uncomfortable	[36]
GI (Greece) (173)	92 unsedated, 87.9 success			Male gender, segmental colonic resection predict success	[37]
GI (Finland) (120)				After the procedure: midazolam *vs* placebo group (30 *vs* 40 mm; P < 0.05; visual analog scale, 0 to 100 mm: 0 = not at all, 100 = extremely).	[38]
GI (Germany) (100)	95 (87 willing to repeat)	As needed sedation (5%)		On a scale of 1 to 9, barium enema and colonoscopy produced similar ratings of discomfort (3.1 *vs* 3.2)	[39]
Surgeons (Singapore) (40)	78 (93 willing to repeat)	As needed sedation	23% required intravenous sedation	Thirty percent had no pain, 55% minimal pain, 8% moderate pain and 3% severe pain	[40]
GI (Japan) (467)	98-99	Variable stiffness (VSC) *vs* standard (CC)		Lower mean pain score was noted in VSC patients compared with CC patients	[45]

negative image[46-49] or acceptance of sedation-risk-free options as a quality indicator[50] is achieved, discussions directed toward encouraging unsedated extended flexible sigmoidoscopy[14,15,51] appear to be a prudent approach to optimize screening and minimize burden. After detailed explanation, if patients and providers accept unsedated flexible sigmoidoscopy as the screening modality, any additional examination of the colon performed during the same session (extended flexible sigmoidoscopy) can benefit the patients. An experienced colonoscopist providing back up polypectomy support to several enodoscopists, simultaneously performing screening by extended flexible sigmoidoscopy is a reasonable model for further heath services research evaluation.

Other approaches such as sedation as-needed (determined by the colonoscopist) and sedation on-demand (at the patient's request) have been reported in community[10,16] and Veterans Affairs (VA)[13,17] practice settings in the US. There is a lower likelihood of coercion with sedation on-demand, as the patient can request medications at any time. Neither, however, can obviate the need for nursing staff and an escort to be available as it cannot be predicted ahead of time which patient will require sedation. Nonetheless, for the patients who can complete without sedation the burden can be avoided. Twenty-eight percent of community[10] and 75% of VA[11] patients accepted the option of sedation on-demand. Amongst these, 77%[11] to 81%[10] completed without sedation and reported minimal discomfort[10,11]. With good bowel preparation, the success rate of cecal intubation

in unsedated colonoscopy provided in the form of as-needed or on-demand sedation is > 90% when attending staff performed the examinations[10,11,16,17].

In the US unscheduled, unsedated colonoscopy has been offered to about 1%-2%[58,59] of patients without an escort. Scheduled, unsedated colonoscopy has been requested by about 6%-7%[16,60] of patients who are educated professionals with independent knowledge of the feasibility of the option. A nursing shortage at the Sepulveda VA led to the introduction of scheduled, unsedated colonoscopy in recent years[4]. The pros and cons of sedation and no sedation (Table 1) are provided to the patient during the pre-endoscopy visit. The colonoscopist will minimize the air insufflated into the colon and keep the length of the colonoscope inside the patient short to decrease discomfort due to distension or stretching of the colon, respectively[61]. During the examination, the colonoscopist will repeatedly inquire about abdominal discomfort, not to remind the patient that the examination should hurt, but to give the colonoscopist a head-start on implementing maneuvers to avert the up-coming discomfort. The patients are also told about the potential need for changing positions and for abdominal compressions to facilitate advancement of the colonoscope. Unsuccessful unsedated colonoscopy may warrant a repeat with sedation. The patients choose either the sedated or unsedated option[4]. The program is an attempt to restore access to the colonoscopy service which was discontinued due to nursing shortage[4], emphasizing patient-centered care and informed choice[12]. Without sedation backup the success rate is only around 80% when usual air insufflation is used[4,5] comparable to that reported overseas[31,36,40]. When a water infusion method in lieu of air insufflation is used, the cecal intubation rate is enhanced to > 90%[5].

Scheduled, unsedated colonoscopy was acceptable to 25%[11] to 30%[4,5] of patients who were interested in communication with the colonoscopist when the option was offered at two VA facilities, one with[11] and one without[4,5] on-site capability to sedate patients. Ninety-eight of 145 patients indicated that the absence of escort requirement was one of the main reasons for their choice of no sedation[4]. Many reflected that had it not been for the option, they would not have been able to participate in screening by colonoscopy or the follow up of the finding of occult blood in their stool[6]. A hypothesis suggested by the latter comment that scheduled, unsedated colonoscopy enhances the effectiveness of other screening modalities deserves to be evaluated. Indeed this approach can complement the solution of arranging escorts proposed to solve the issue of lack of escorts in an inner city screening program with low compliance[62]. The experience of scheduled, unsedated colonoscopy[4,5,12,13] cannot be generalized to the US screening population at large since the data are derived from veterans (> 95% men) without complex pelvic anatomy, pathology and pain threshold. Another view opposing scheduled, unsedated colonoscopy is that the emphasis on practice efficiency and economics in the US[20] dictates that the endoscopist should not be spending extra time talking to the patient in spite of the positive gains from having no sedation. We propose unsedated colonoscopy as an option that patients can accept or decline, without coercion from the colonoscopist. For diagnostic colonoscopy, any and all potential burdens of sedation[2,57] are acceptable. The definition of screening involves application of a test in asymptomatic and otherwise healthy individuals. The potential burden of sedation[2,57] may not be justifiable if an individual is willing to accept unsedated colonoscopy for screening.

As described above, in US patients who choose the options, the success rate is high. A strategy that will permit individuals with the potential ability to complete colonoscopy without sedation to access unsedated or sedation on-demand colonoscopy will translate into many who can avoid the direct and indirect costs of sedation. A cost-effectiveness analysis based on the proper perspective, however, remains to be performed and reported. The real challenge is to convince practicing colonoscopists in the US to consider a "less burdensome approach" for patients willing to undergo unsedated colonoscopy. Data can then be collected to compare the cost and the effectiveness of sedated and unsedated colonoscopy.

In unsedated patients, a limitation to cecal intubation is discomfort[4,36]. Complementary alternative medicine approaches to minimize discomfort include hypnosis[63] and listening to music[64]. Mechanical techniques including magnetic endoscopic imaging[43,65] and small caliber over tube-assisted[66] colonoscopy can attenuate discomfort in the unsedated patients. Water immersion[24,67,68] and warm water infusion in lieu of air insufflation[5,13,69-71] techniques have shown promise in minimizing discomfort and the need for sedation. The efficacy, acceptance by patients and colonoscopists, and the practicality of trainee education[68] should be evaluated to determine the feasibility of implementation by future practitioners.

Family practice programs in the US have embraced the teaching of unsedated colonoscopy[72]. However, they constitute only a small fraction of such trainee procedural education. Paradoxically, the education of gastrointestinal (GI) trainees in unsedated colonoscopy has been deemed impractical[16]. Serendipitously, the incorporation of unsedated colonoscopy into our training program revealed that the involvement of GI trainees in routine unsedated colonoscopy was feasible[4]. These observations suggest that the appropriateness of the US Accreditation Council for Graduate Medical Education 2005[73] in continuing to exclude the learning of unsedated colonoscopy from the GI trainee curriculum deserves to be reexamined. The hypothesis that teaching the superior skills needed for "unsedated colonoscopy" at the trainee stage deserves to be evaluated further[6]. Whilst more challenging at that time, this should become a very good investment in the longer-run - likely to

reduce complications, increase accuracy, and lower the burden of sedation for individual patients.

EXPERT COMMENTARIES

The next section is devoted to commentaries from around the world (arranged in alphabetical order of co-authors) provided by expert colonoscopists who have reported on their experience of providing unsedated colonoscopy to their patients or themselves accepted the option and underwent unsedated colonoscopy.

Dr. Aljebreen (Riyadh, Saudi Arabia)

Although the feasibility of unsedated colonoscopy is well established, it's not uncommon to hear that "it is inhumane" when this issue is discussed among colleagues. There are many reasons why some patients prefer to undergo colonoscopy without sedation. In our experience[31], no escort requirement, fear of the usual sedation-related complications and restrictions on activities for almost one full day are the common reasons why patients choose unsedated colonoscopy. There is a subset of patients who feels the risk of perforation might be higher with sedated colonoscopy because of the absence of the warning sign of pain. They prefer unsedated over sedated colonoscopy to avoid this risk. Whether this difference is real or not deserves to be evaluated in future studies. There is another group of patients who want to know the result of their colonoscopy on the spot and who don't want to feel anxious waiting for their next visit. On the other hand, in addition to fear of pain one of the most common reasons for choosing sedated over unsedated colonoscopy is the embarrassment associated with the endoscopist being of a different gender. Contrary to the belief of many endoscopists, the time to reach the cecum is comparable in sedated and unsedated colonoscopy (12 min and 11.7 min, respectively). There is, however, a big difference in the total time from admission to discharge (83 min and 21 min, respectively) (our unpublished data). When time is taken to address these differences with the patients, many would consider unsedated colonoscopy.

Dr. Brocchi (Bologna, Italy)

The evidence discussed above suggests colonoscopy without routine sedation is a plausible approach. Its application does vary widely among countries and cultures, ranging from routine to an uncommon practice. In non-sedated patients, procedure-related discomfort limits cecal intubation when traditional air insufflation is used. Various methods including water-related adjunct techniques contribute to overcoming this limitation. Less or no sedation are possible when these water-related techniques are used, even in settings where sedation is routine, without compromising patient satisfaction or quality of the examination (e.g. cecal intubation rates, adenoma detection rates, complication rates). In our experience, whether unsedated colonoscopy is employed or not depends on a variety of endoscopist and patient factors. In the endoscopists' view, major favourable points are the lack of sedation-related complications, the gaining of time in the turn-over of patients and the lack of adjunctive nurse requirement for the recovery room (with decreased institutional costs). On the other hand, endoscopists have to spend some time to reassure patients that the unsedated examination is not too unpleasant and that sedatives or analgesics may be given at any time during the examination in case of discomfort or pain. Furthermore, the possibility of losing an unsatisfied patient may play in favour of sedation in the mind of endoscopists. The major patient argument against no sedation is the fear of discomfort or pain during the examination, making the possible advantages after a sedation-free examination (e.g. no need for an escort and no activity restrictions, in particular driving) less important from their point of view .

To take full advantage of the opportunities offered by this new approach, in our Endoscopy Unit[24] we have adopted a policy of starting colonoscopy without sedation, but with an intravenous catheter always inserted. Patients are reassured regarding the possibility of receiving drugs at any time during the examination, in case of discomfort or pain. This simple approach, in our experience, reassures and calms the patient, making them more cooperative during the examination. We always employ the warm water method with minimal air insufflation. Intravenous drugs are given, at the discretion of the endoscopist, when patients show signs of substantial pain or when significant technical difficulties are encountered (e.g. in cases of an angulated colon). Patients are sometimes asked to bear some pain for a short time. In this way, we have decreased significantly the number of patients requiring conscious sedation and the amount of sedatives used. Notably, we performed our study mostly on unselected patients, thus the results are largely applicable to our daily endoscopic practice. In our opinion, this approach could be a good balance between an over- or under-use of drugs during colonoscopy. Lastly, we wish to underline another practical point as we have noted a tendency towards an increase in colonoscopy requests (now in our Unit the requests ratio for endoscopies -gastroscopies versus colonoscopies - is about 1:3/1:4). This is probably due to an increasing awareness of the importance of colorectal cancer screening. If this is confirmed in the near future, endoscopy units will face increasing demand for their services. The hypothesis that the use of colonoscopy without routine sedation combined with water-related techniques may enhance performance and productivity deserves to be tested.

Dr. Liao (Taipei, Taiwan, China)

In Taiwan, the costs of screening colonoscopy and sedation are US$75 and US$100 respectively and are not reimbursed by insurance. Besides being expensive,

sedation significantly increases the demand on medical resources and personnel, limiting the use of colonoscopy in Taiwan. In a prospective evaluation of the feasibility of primary screening with unsedated colonoscopy, we found that it was well accepted in nine-tenths of examinees who chose this option[22]. If this knowledge can become more widely known through adequate education and counseling and, as a result, sedation is not administered routinely, screening colonoscopy may become more affordable and available in Taiwan. We have also noted a significant association between the individual endoscopist and the pain and need for sedation during colonoscopy[22], a finding that is generally well recognized but has not been proven. Therefore, more attention to unsedated colonoscopy in endoscopy training may increase its acceptance and use. This will be necessary to make unsedated colonoscopy more widely accepted.

Dr. Mizukami (Yokohama, Japan)

I believe that sedation is not necessary for routine colonoscopy except in patients with severe mental illness. The collapse-submergence method for insertion described by us[68] causes hardly any pain in most unsedated patients in Japan. Almost 100% of the colonoscopy in our hospital (Yokohama Municipal Citizen's Hospital, Japan) has been performed without sedation. I believe that pain during colonoscopy indicates the risk of perforation and that sedation masks this important warning. I think that a painless unsedated colonoscope insertion technique is essential for patient safety. The collapse-submergence method minimizes colonic distension by water infusion and allows complete removal of air when the tip of the colonoscope is in the rectosigmoid location. These maneuvers straighten the rectosigmoid colon to enable the colonoscope to be inserted without causing looping of the colon[68]. The volume changes in the colon during colonoscopy were measured. The total volume of residual gas removed from the rectum and sigmoid colon in our subjects was 205 ± 28 mL (mean ± SD, n = 3). The average volume of water infused was 234 ± 19 mL (n = 11), and that of the fluid aspirated during the scope insertion was 441 ± 62 mL. This negative balance is considered favorable for the examination. We asked 21 patients to report their discomfort just after the colonoscopy using the following scale: grade 1, nothing wrong; grade 2, strange feeling; grade 3, distension of the abdomen; grade 4, tolerable pain; and grade 5, intolerable pain. The median self-reported score was grade 2 [grade 1, grade 3, (25%, 75%, respectively)]. In our experience even trainees can perform painless unsedated colonoscopy from the outset. We have demonstrated the ease of mastering of the technique by trainee endoscopists, as follows. Under my supervision, 6 novices with only experience in upper gastrointestinal endoscopy inserted the colonoscope by this method in 1 patient per week. As long as the patients did not complain of pain they were allowed 10 min to accomplish the insertion. The first cecal intubation within 10 min was accomplished after an average number of 3.3 patients. The average success rate of cecal intubation during the first 3 mo was 59%.

Dr. Triantafyllou (Athens, Greece)

In Greece, up to 20% of the colonoscopies are performed on totally unsedated patients. However, sedation on patient demand or when judged necessary by the endoscopist is given in the majority of cases, leaving only a small percentage of scheduled, sedated examinations. In 2000, Professor Ladas showed, in his private facility, a colonoscopy completion rate of just below 90% with small amounts of sedation given to less than 10% of the patients. He proposed that male gender and segmental bowel resection are good predictors of successful sedationless colonoscopy[37]. Eight years later we performed a quality assurance audit in our academic center, where sedation was given in only 40% of the patients. When we excluded cases with organic bowel obstruction, the total colonoscopy completion rate was 88.2%. Moreover, in colorectal cancer prevention cases (index or surveillance examinations) this rate was 92.4%. Use of sedation - analgesia was associated with a 3.8% increase in the colonoscopy completion rate but this benefit was compensated by a significant increase of adverse reactions, which were all mild[74]. Therefore, we are in the process of setting up a study for patients in such a way that they will have the option of receiving sedation. Colonoscopy will start with no sedation but medication can be given either on patient demand during the examination or if the endoscopist decides to continue the exam with the patient sedated. The study's primary endpoint will be the percentage of patients achieving colonoscopy to the cecum without sedation in the two groups of patients: conventional instrument insertion with air vs. water assisted insertion. We shall compare our results with those of others with comparable designs in different locations around the world. The results will shed light on similarities and differences in diverse cultural settings.

Dr. Chang (Chicago, IL, United States)

I have now had about four colonoscopies, all unsedated, following the finding of a malignant polyp. Each was uneventful and easily tolerated. In every instance, the procedure was performed by a skilled colonoscopist who was judicious with insufflation and navigation. The duration of the entire procedure was in fact shorter than sedated colonoscopy because detailed preparation and recovery periods were not required. I was able to return to work immediately. My positive experience with unsedated colonoscopy can be attributed to two factors. First, each procedure was performed by a skilled endoscopist. Second, my state of mind - I knew what to expect and experienced minimal anxiety during the procedure.

Dr. Schapiro (Encino, United States)

Due to my strong family history of colon cancer I

have had eight colonoscopies during the past 30 or so years and seven of these have been unsedated. I have also performed many thousands of colonoscopies, a small percentage of which have not used sedation. I am a firm believer that unsedated colonoscopy is a safe and effective approach that is vastly underutilized. However, the primary problem resides at the beginning training level where (at least in this country) sedated colonoscopy is the standard of practice. Not only does this hinder the unsedated approach, but does not allow the early development of "painless" colonoscopy as technique (loop removal) is less emphasized. The vast number of community colonoscopists get over discomfort by forming larger loops than are required for unsedated colonoscopy. I feel that the concept of unsedated colonoscopy needs to be part of the early training experience and then patients can be offered this as the primary alternative by physicians who believe in their ability to offer "painless" colonoscopy. There are of course other obstacles mostly related to patient's preconceived fear of rectal intubation. I feel that will be overcome with proper education of the lay population.

DISCUSSION

The above review indicates that sedation-risk-free colonoscopy adequately depicts the potential of unsedated colonoscopy to minimize patient burden due to sedation in screening examinations. It is feasible not only worldwide, but also in the US. Colonoscopists describe the pros and cons and offer it as an option that the patient can accept or decline without coercion, based on their needs and preferences. A water method developed to minimize discomfort has shown promise in enhancing outcomes of unsedated colonoscopy.

No colonoscopist, particularly those who are against or uncomfortable with sedation-risk-free colonoscopy, should feel compelled to offer this option to his/her patients in the US. By the same token, she/he should not stand in the way of progress towards patient-centered care focused on minimizing patient burden. Our first-hand experience is that the requirements (escort, time commitment) of sedation for colonoscopy clearly preclude patients with limited resources (lack an escort, cannot afford to take time off from work) from participation in screening colonoscopy. Our opinion, backed by data in the literature and expert commentaries, is that even in the US, unsedated colonoscopy is an option that can close the gap between disparity subgroups. It is also an option that patients can reject if it does not meet their needs. On the other hand, it is an option that some patients can use to allow them to participate in the screening that we recommend. Since the unsedated option is non-standard practice in the US, we included commentaries by expert colonoscopists from around the world provided. They have reported on their experience of providing unsedated colonoscopy to their patients or accepted the option for their own screening. The technique received endorsement in both cases.

In conclusion, the use of scheduled, unsedated colonoscopy in the US appears to be feasible for colorectal cancer screening. Studies to assess its applicability in diverse practice settings deserve to be conducted and supported.

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GUIDELINES FOR CLINICAL PRACTICE

A new breakthrough: ESD using a newly developed grasping type scissor forceps for early gastrointestinal tract neoplasms

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Abstract

Endoscopic submucosal dissection (ESD) has allowed the achievement of histologically curative en bloc resection of gastrointestinal neoplasms regardless of size, permitting the resection of previously non-resectable tumors. The ESD technique for treatment of early gastric cancer has spread rapidly in Japan and a few other Asian countries due to its excellent eradication rate compared to endoscopic mucosal resection. Although numerous electrosurgical knives have been developed for ESD, technical difficulties and high complication rates (bleeding and perforation) have limited their use worldwide. We developed the grasping type scissor forceps (GSF) to resolve such ESD-related problems. Our animal and preliminary clinical studies showed that ESD using GSF is a safe (no intraoperative complication) and technically efficient (curative en bloc resection rate 92%) method for dissection of early gastrointestinal tumors. The use of GSF is a promising option for performing ESD on early stage GI tract tumors both safely and effectively.

INTRODUCTION

The Endoscopic submucosal dissection (ESD) technique introduced by Hirao *et al*[1] has subsequently been modified by several investigators, allowing curative en bloc resection of broad superficial tumors with the use of special cutting knives. It has been reported that ESD improves the rate of successful en bloc resection in early stage gastrointestinal neoplasm as compared with endoscopic mucosal resection (EMR)[2-7]. However, ESD using knives is technically difficult and carries a high risk of perforation and bleeding. Complication rates with knives for the dissection of gastric tumor are reported to be 0% to 70%[4,8-12]. Incision using knife devices merely provides contact between the knife and the tissue and cuts using an electrosurgical current. These cutting processes do not fix the device to the targeted tissue, making it difficult to accurately place the knife during electrosurgical incision because of bodily motions such as cardiac or respiratory movement[13]. Lack of fixation and compression effects can cause unexpected incision and insufficient coagulation and result in major

complications such as perforation and bleeding. We believe that the most effective and simplest way of avoiding such complications is to grasp and incise the targeted tissue using an electrosurgical current. We have therefore developed a new grasping type scissor forceps (GSF) which can grasp and incise the targeted tissue using an electrosurgical current[13-18]. In this article we describe the concepts of development, clinical outcomes in ESD and future potential of this new device.

CLINICAL OUTCOMES OF ESD USING CONVENTIONAL KNIFE DEVICES

Recent results of en bloc resection rate of ESD for neoplasms in the esophagus, stomach and colorectum are 95%-100%, 76%-96% and 77%-98.6% respectively[4]. On the other hand, reported bleeding and perforation rate of ESD for neoplasms in the esophagus, stomach and colorectum are 0% and 6.9%, 0%-40% and 0%-50%, and 0%-12% and 1.4%-10% respectively[4,8,12,19-21]. Current ESD using knife devices shows high tumor eradication rates but substantial risks during the procedure.

THEORETICAL PROBLEMS OF ESD USING CONVENTIONAL KNIFE DEVICES

At present, numerous electrosurgical knives such as the diathermic needle knife[3,22], insulation-tipped electrosurgical knife (IT)[2], hook knife[23], flex knife[10], triangle-tipped knife[24], flush knife[25], fork knife[19], and mucosectome[20] are available for ESD (Figure 1). During ESD using conventional knife devices, problems may be encountered i.e. unintentional incision due to bodily motions, perforation due to thin gut wall and bleeding. Our proposed measures for each problem are shown in Table 1. We consider that the shortcomings of current knives are deficiency of fixing and lift up, compression to the targeted tissue and outside insulation. Therefore we developed a grasping type scissor forceps (Figures 1 and 2) to overcome the shortcomings of conventional knife devices[13-18].

NEWLY DEVELOPED GRASPING TYPE SCISSOR FORCEPS

The grasping type scissor forceps (GSF) (XDP2618DT, Fujifilm Corporation, Saitama, Japan) (Figure 2)[13-18] can grasp and cut a piece of tissue with an electrosurgical current. It has a 0.4 mm wide and 4 mm or 6 mm long serrated cutting edge to facilitate grasping the tissue. The outer side of the forceps is insulated so that electrosurgical current energy is concentrated at the blade to avoid burning the surrounding tissue. Furthermore, the forceps can be rotated to the desired orientation. The diameter of the forceps is 2.7 mm. The GSF is available for a standard endoscope with working channel width of 2.8 mm or over. This device is disposable and not reusable and is used for circumferential marginal incision, submucosal dissection and hemostatic treatment. The autocut mode (ICC 200; Erbe, Tübingen, Germany) 120W (effect 3) is used for cutting (circumferential incision and submucosal excision) and the soft coagulation mode 70W (effect 3) is used for hemostatic coagulation.

Table 1 Problems during ESD using conventional knives and proposed measures

Problems	Proposed measures
Unintentional incision	Device fixation to the targeted tissue
	Outside insulation
Perforation	Sufficient submucosal injection
	Outside insulation
	Lift up the targeted tissue by device
	Good visualization of the targeted area
Bleeding	Compression of the blood vessel by device

ESD: Endoscopic submucosal dissection.

In our previous animal study (porcine stomach)[13], we resected three specimens safely and easily with no unintentional incision by ESD using the GSF. The histological analysis of the ulcers due to the procedure showed shallow submucosal ulcers without perforation and excessive burning. All clinical studies[14-18] described in this article were reviewed and approved by the ethics committee of Aso Iizuka Hospital.

TECHNIQUES OF ESD USING GSF

ESD technique using GSF is as follows (Figure 3). Circumferential markings are made by using a hook knife (KD-620LR, Olympus) with coagulation current 20-40W created by an electrosurgical generator (ICC 200; Erbe, Tübingen, Germany) (Figure 4A). Next, 10% glycerin with 0.9% NaCl and 5% fructose (Glyceol; Chugai Pharmaceutical Co., Tokyo, Japan) or hyaluronic acid solution (MucoUp: Johnson and Johnson Co., Tokyo, Japan) is injected into the submucosal layer to lift up the lesion. The lesion is separated from the surrounding normal mucosa following complete incision around the lesion using the GSF (Figure 4B and C), A piece of submucosal tissue is grasped, lifted up and cut with the GSF using electrosurgical current to achieve submucosal excision (Figure 4D). Finally, the lesion is completely resected (en bloc resection) by GSF (Figure 4E and F). Treatment of bleeding during the procedure is done by coagulation with the GSF (Soft coagulation mode 70W, effect 3). Prophylactic coagulation of visible vessels is carried out using GSF (Soft coagulation mode 70W, effect 3).

CLINICAL OUTCOMES OF ESD USING GSF IN OUR PRELIMINARY STUDIES

Clinicopathological characteristics of the lesions treated by ESD using GSF[17,18] are summarized in Table

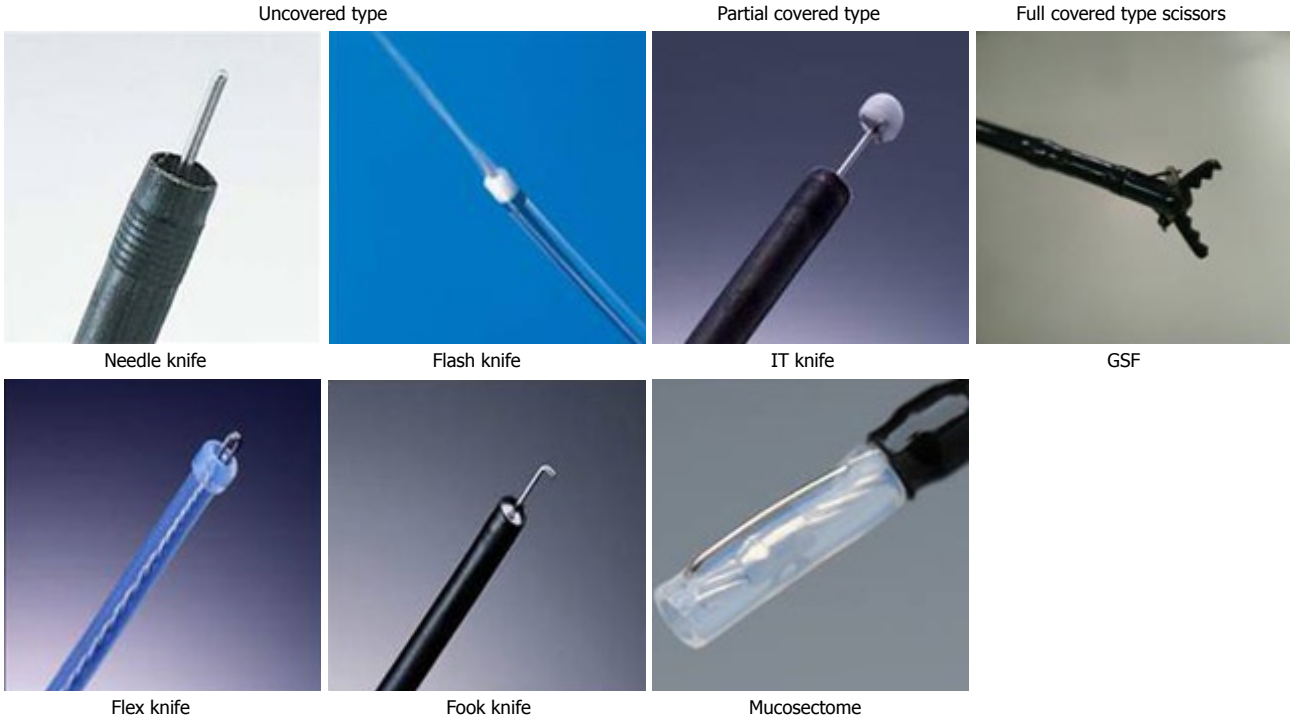

Figure 1 Several endoscopic cutting devices have been developed in Japan. They are divided into 3 broad categories as above: Uncovered type knife, partial-covered type knife, and full-covered type scissors.

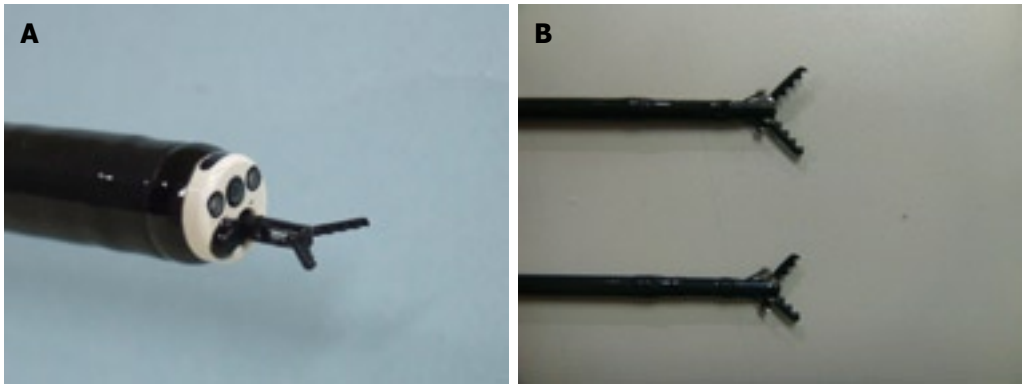

Figure 2 Grasping type scissor forceps (GSF). A: Distal tip of the long type GSF. The outer side of the forceps is insulated so that electrosurgical current energy is concentrated at the blade to avoid burning to the surrounding tissue (closed discharge). B: Long type (upper side image: 6mm) and short type (lower side image: 4 mm) GSF.

2. All lesions were treated simply and safely with no unexpected incision by a beginner endoscopist in ESD. The grasping and lift up steps before cutting the targeted tissue provided good visualization of the interest and allowed the use of sufficient pre-cut coagulation. The technical outcome[17,18] is summarized in Table 3. The mean size of the epithelial tumors and resected specimens was 16.6 ± 9.0 mm and 33.0 ± 10.5 mm respectively. The curative en bloc resection rates according to tumor location were 100% (3/3) in the esophagus, 97% (34/35) in the stomach[17], 80% (8/10) in the colon and rectum[18] and 92% (45/49) overall. All lesions were resected in en bloc fashion endoscopically. Four cases (8%) were judged as histologically positive margin of the tumor cells due to burning effect. The mean operating time according to tumor location was 74.7 ± 26.3 min in the esophagus, 104.1 ± 54.4 min in the stomach[17], 154.9 ± 83.6 min in the colon and rectum[18] and 114.0 ± 63.4 min overall.

No intra-operative severe complications (perforation or uncontrollable bleeding) occurred and post-operative bleeding was seen in 2% (1 of 49) of cases.

THEORETICAL ADVANTAGES OF GSF AS COMPARED TO CONVENTIONAL KNIFE DEVICES

Safety

GSF can grasp the targeted tissue. The grasping step has three safe effects: (1) fixation, (2) lift-up effect and (3) compression effect (Table 4, Figure 5). (1) The grasping step prior to electrosurgical incision provides fixation of the device to the targeted tissue to avoid unintentional incision[13-18]. GSF has a thin serrated cutting edge and an insulated coating of the outer side of the forceps. These characteristics facilitate grasping the targeted tissue and concentrate electrosurgical current energy

Table 2 Clinicopathological characteristics (n = 49)

Gender, male/female			32/17
Mean age years (range)			69 (31-87)
Location, *n*	Esophagus		3
		Middle	1
		Lower	2
	Stomach[17]		35
		Upper	9
		Middle	8
		Lower	18
	Duodenum	Bulbus	1
	Colorectum[18]		10
		Cecum	2
		Ascending	1
		Transverse	2
		Descending	2
		Rectum	3
Histologic type and depth of invasion, *n*			
	Carcinoma		27
		Mucosa	24
		Superficial submucosa	2
		Deep submucosa	1
	Adenoma	Mucosa	20
	Carcinoid tumor	Deep submucosa	1
	Granular cell tumor	Deep submucosa	1

Table 3 Technical results of ESD using GSF (n = 49)

Curative en-bloc resection rate, Total	92% (45/49)
Esophagus	100% (3/3)
Stomach[17]	97% (34/35)
Duodenum	(0/1)
Colon and rectum[18]	80% (8/10)
Mean ± SD operating time, minutes (Range), Total	114.0 ± 63.4 (33-337)
Esophagus	74.7 ± 26.3 (59-105)
Stomach[17]	104.1 ± 54.4 (33-264)
Duodenum	172
Colon and rectum[18]	154.9 ± 83.6 (70-337)
Mean ± SD size of tumor size, mm (Range)	16.6 ± 9.0 (5-43)
Mean ± SD size of resected specimen, mm (Range)	33.0 ± 10.5 (15-60)
Intra-operative perforation rate	0/49 (0%)
Intra-operative major bleeding rate	0/49 (0%)
Postoperative bleeding rate	1/49 (2%)
Postoperative perforation rate	0/49 (0%)

GSF: Grasping type scissor forceps.

at the blade to avoid burning the surrounding tissue (closed discharge). (2) It also has a lift up effect on the targeted tissue which can sufficiently separate grasped tissue from the underlying proper muscle layer before incision and contributes to preventing perforation. The grasping and lift up steps before cutting the targeted tissue provides good visualization of the interest and allows the use of sufficient pre-cut coagulation[13-18]. (3) GSF has a compression effect which is effective for pre-cut coagulation and hemostatic treatment of post-cut hemorrhage. GSF can be used to grasp the targeted tissue again if the grasped site is inadequate before electrosurgical cutting[13-18]. We think that these merits

Table 4 Theoretical advantages of GSF during ESD

Advantageous mechanism	Expected physical effects	Technical outcome
Grasp	Fix	(1) No unintentional incision
	Lift-up	(2) Good visualization
		(3) Sufficient separation from the underlying proper muscle layer to prevent perforation
	Compress	(4) Hemostatic effect to prevent and treat bleeding
Outside insulation	Closed discharge	(5) Minimizing damage to the surrounding tissue to prevent perforation
Rotatable	Change the direction of grasping	(6) Facilitating accurate targeting

reduce the chance of unintentional incisions, bleeding and other severe complications.

Simplicity

Each step of ESD (circumferential incision, submucosal excision, hemostatic treatment) can be achieved by the following three operations: (1) grasping the targeted tissue (fixation), (2) lifting up the grasped tissue (separation of the grasped tissue from the underlying proper muscle layer) and (3) cutting the grasped tissue (or coagulating the blood vessel) using an electrosurgical current. These operations are simple and as easy as a bite biopsy technique.

Facility for training of ESD

ESD using GSF is safe and simple. In our preliminary studies[17,18] all cases were safely and effectively resected using this method by a beginner endoscopist in ESD. Furthermore, in the grasping confirmation step we could sufficiently discuss the adequacy of the grasped tissue with the attending endoscopist prior to incision using electrosurgical current. This precut confirmation step is the greatest advantage of our method and is useful for safety and for training in ESD.

CURRENT DISADVANTAGES OF ESD USING GSF

The procedure time of ESD using GSF was longer than the reported times using knife devices[4,26-30]. The main reasons were (1) these clinical trials were performed by a beginner in ESD (The endoscopist was the inventor of GSF with prior experience of only seven cases of conventional ESD) and (2) the frequent difficulties in rotating the GSF to the desired orientation during

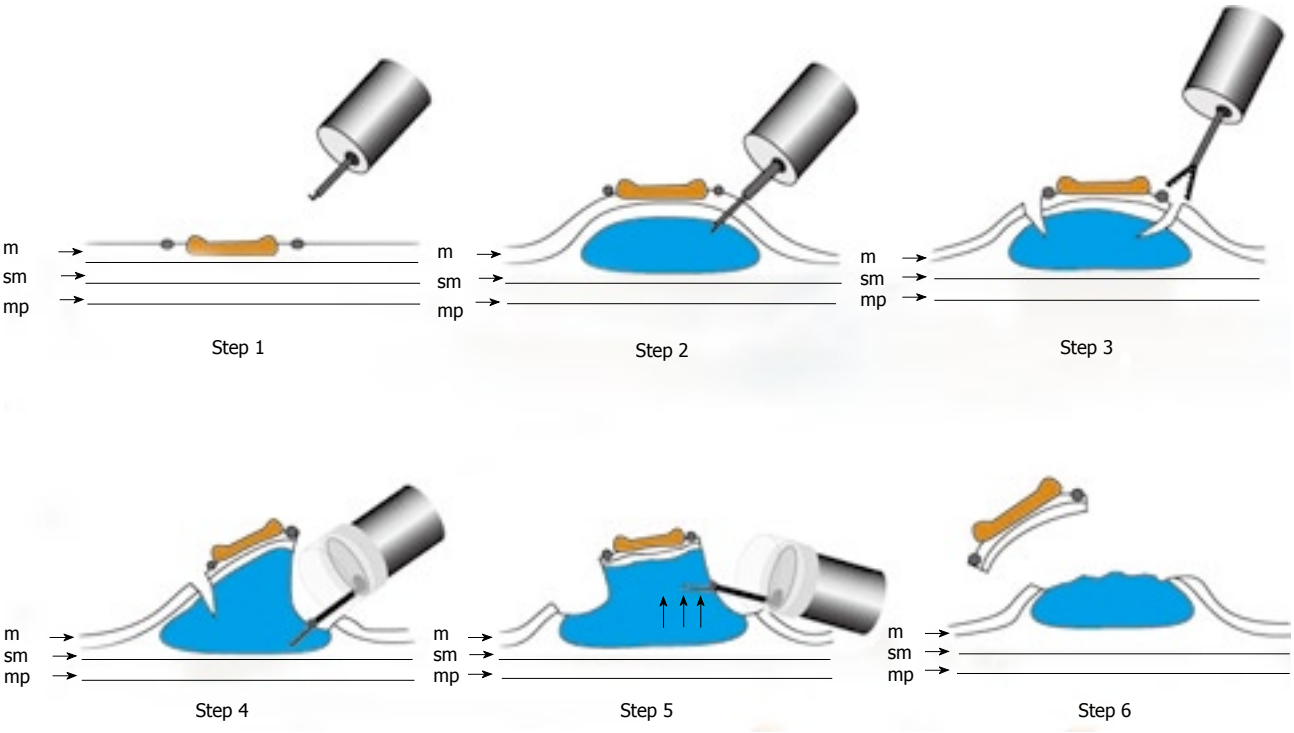

Figure 3 Schematic shows ESD using GSF. Step 1: Marking dots are made on the circumference of the lesion to outline the incision line; Step 2: A concentrated glycerin solution mixed with a small volume of epinephrine and indigo carmine dye is injected into the submucosal layer around the target lesion to lift the entire lesion; Step 3: The lesion is separated from the surrounding normal mucosa by complete incision around the lesion using the GSF; Step 4: A piece of submucosal tissue is grasped by GSF; Step5: A grasped tissue is lifted up and cut with the GSF using electrosurgical current to effect submucosal exfoliation; Step 6: The lesion is resected in one piece; m: Mucosa; sm: Submucosa; mp: Muscularis propria.

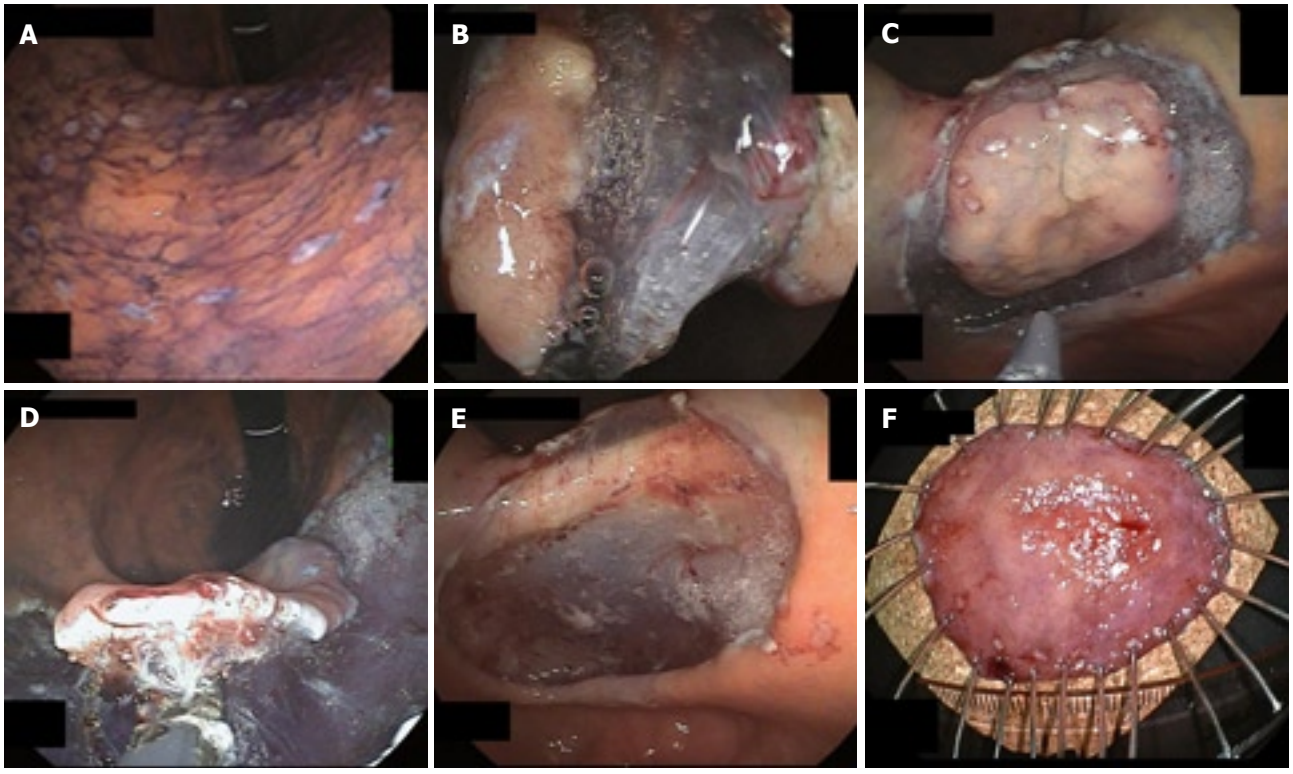

Figure 4 Endoscopic view of the procedure of ESD using GSF. A: Marks are made at several points along the outline of the lesion with a coagulation current; B: The mucosa is incised outside the marker dots to separate the lesion from the surrounding non-neoplastic mucosa using GSF; C: Completion of the GSF cutting around the lesion with a safe lateral margin; D: The submucosal connective tissue beneath the lesion is grasped and lifted up and excised using GSF from the underlying muscle layer; E: The lesion is cut completely from the muscle layer; F: The resected specimen showing en bloc resection of the lesion.

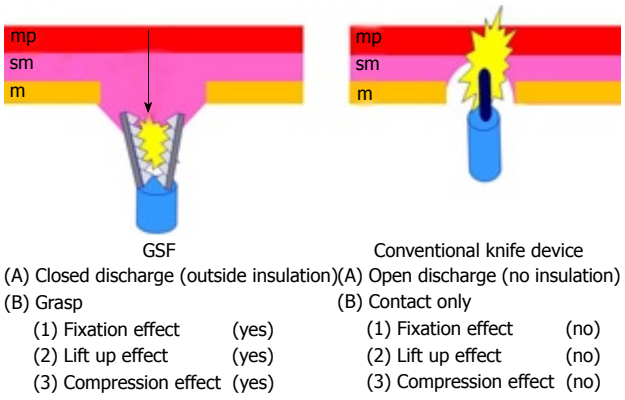

Figure 5 Mechanical differences between GSF and conventional knife devices. sm: Submucosa; mp: Muscularis propria.

a retroflex approach. A significant learning curve is associated with achieving proficiency in ESD[31]. Probst *et al*[32] showed a learning curve resulting in a decreasing procedural duration and an increasing rate of complete en bloc resection over time. Procedure time will be shortened in the near future by the learning curve in ESD using GSF and a solution to the problem of rotating the GSF by further mechanical refinement.

FUTURE POTENTIAL

From recent studies, ESD shows a higher tumor eradication rate than conventional EMR irrespective of tumor size[4,33-37]. However, ESD using conventional knife devices requires highly skilled endoscopists and a sufficient training program is required for permeation of this technique[31,32]. At present because of this requirement, the merits of ESD can be obtained in only a few advanced institutions in Japan and several other Asian countries[4,12,21,26]. Because of its safety and simplicity, we believe that ESD using GSF will become widely accepted for use throughout the world[17,18]. We hope to expand the application of this procedure to decrease the complications associated with ESD. However, further refinements and experiences of this method are needed in order to more easily achieve the curative en bloc resection of early GI tract tumor. Furthermore, extensive controlled, randomized studies in controlling ESD-related complications e.g. *vs* IT knife, *vs* needle knife or *vs* other conventional devices are necessary to fully evaluate the usefulness of our new device.

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REVIEW

Management of difficult bile duct cannulation in ERCP

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Abstract

In Encoscopic Retrograde Cholangiopancreatography (ERCP), the main concern is to gain access into the bile duct while avoiding the pancreatic duct because of the risk of post-ERCP pancreatitis. Difficult cannulation is defined as a situation where the endoscopist, using his/her regularly used cannulation technique, fails within a certain time limit or after a certain number of unsuccessful attempts. Different methods have been developed to manage difficult cannulation. The most common solution is to perform a precut papillotomy either with a needle knife or with a sphincterotome with or without a guide wire. This review describes different methods to overcome cases of difficult cannulation. We will discuss the success rate and complication rates associated with different methods of reaching the biliary tract.

Key words: Endoscopic retrograde cholangiopancreatography; Difficult cannulation; Sphincterotomy; Precut; Complication

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INTRODUCTION

This review intends to describe the current situation of so-called difficult cannulation, in endoscopic retrograde cholangiopancreatography (ERCP). Definitions of difficult cannulation vary in reports. There is no established time limit or limits to unsuccessful attempts before the cannulation is termed difficult. The type of primary tool used for cannulation is associated with different success rates and varies according to the preferences of a particular endoscopist (Table 1).

Solutions for overcoming difficult cannulation vary depending on the practices of the endoscopist. Various methods have been developed to manage difficult cannulation and, in addition, to try to avoid the ever-present threat of post-ERCP pancreatitis. The main tools used range from standard catheters to guide-wire-assisted rotatable papillotomes. The most commonly used solution in a difficult situation is to perform a precut (access) papillotomy either with a needle knife or a sphincterotome with or without a guide wire.

For a literature review, a Medline search (keywords for search: difficult cannulation, ERCP complication, precut, needle-knife, post-ERCP pancreatitis) for the years 1990-2009 was performed. The reference list of this review is by no means comprehensive and several good reports are not mentioned. An attempt has been made to include those representative references that contain a typical example of one type of definition, tool or solution to the problem.

DEFINITION

Difficult cannulation is defined as a situation where the endoscopist, using his/her regularly used cannulation

Table 1 Tools and methods for cannulation

Standard techniques
Catheters:
Standard
Steerable
With or without guide wire
Sphincterotomes:
Single or multi-lumen
Rotatable
With or without guide wire
Guidewires:
Nitinol
Hydrophilic
Advanced techniques without precut
Double wire technique
Over pancreatic stent
Precut access with
Needle knife:
Starting at orifice
Fistulotomy above orifice
Over pancreatic stent
Sphincterotome:
Erlangen sphincterotome
Transpancreatic with guide wire
Papillectomy for duct access
EndoUS-guided biliary access

technique, fails within a certain time limit or after a certain number of unsuccessful attempts and hence resorts to precutting in order to achieve deep cannulation of the biliary duct.

In ERCP, because of the risk of post-ERCP pancreatitis the main concern is to gain access into the bile duct while avoiding the pancreatic duct. The difference between success in cannulation and the point where the situation is considered difficult depends on the tools used and on the arbitrarily set time limit. Cannulation of the pancreatic duct may be more difficult than gaining access into the bile duct. However, difficult cannulation specifically refers to the situation where bile duct entry is challenging.

The reported time limits within which the regularly used cannulation technique is abandoned vary between 10 and 30 min[1-6]. The 15- to 30-min limits are used less consistently[7-12].

In addition to time, when defining difficulty the number of passages or contrast injections into the pancreatic duct must also be considered. The strictest limits within the arbitrarily set time have been three to five passages or injections into the pancreatic duct. Even if those entries have occurred before the set time limit has expired, the procedure is recognized as being difficult cannulation[1,2,6,12,13]. Few reports have accepted multiple entries into the pancreatic duct within the time limit[7,10]. In several reports where the time was not specified, the only limiting factor was the number of allowed attempts on the papilla, between five and ten[14,15].

COMPLICATIONS AND RISK OF DIFFICULT CANNULATION IN ERCP

The rate of severe or fatal complications associated with ERCP is low where experienced personnel at high-volume centres are involved. In Charleston, South Carolina, over a 12-year period 11497 ERCPs were performed; 42 (0.36%) patients experienced severe and 7 (0.006%) fatal complications[16]. The frequency of severe and fatal complications associated with ERCP at another single specialized surgical high-volume referral centre where 2555 patients had undergone the procedure revealed 17 severe complications (0.7%) and a procedure-related mortality rate of 0.08% in 9 years[17].

A difficult cannulation alone has been shown to carry an inherent risk for a post-ERCP complication[18-20]. Freeman et al. prospectively studied 1963 consecutive patients at 11 centres in the United States[19]. The risk of pancreatitis after a difficult cannulation compared with a standard cannulation increased from 4.3% to 11.3%. In a single-centre study involving 1223 patients, the risk of pancreatitis after a difficult cannulation was 14.9%, compared with a rate of 3.3% for a standard cannulation[20]. Possible reasons for the increased risk of pancreatitis may be excessive manipulation, resulting in mechanical trauma and oedema of the pancreatic sphincter, or repeated contrast medium injections into the pancreatic duct[19]. In one study, two or more pancreatic duct injections with contrast material were shown to be a significant risk factor for post-ERCP pancreatitis[21]. On the other hand, in the Halttunen *et al*[22] study, the number of contrast injections was not confirmed to be a risk factor for post-ERCP pancreatitis.

In a Chinese multi-centre study[23], a cannulation time exceeding 10 min, one or more pancreatic duct wire passes, and needle-knife precutting were risk factors for ERCP-related complications. Similarly, in an Italian multicentre study of 2769 patients in 9 centres, a small centre size and precutting were independent risk factors for complications after therapeutic ERCP. In this study, small centres exhibited increased technical failures, ERCPs had to be repeated more often and precutting techniques were used more frequently[24]. When the learning curve of a single endoscopist was studied, the need for precut sphincterotomy decreased with increasing ERCP experience. The complication rate of precutting remained at 12%-14% throughout the study period[25].

Using the guide-wire technique for bile duct cannulation may lower the likelihood of post-ERCP pancreatitis by facilitating cannulation and reducing the need for a precut sphincterotomy. As reported by Lella *et al*[26], there was no pancreatitis in the guide-wire group of 200 patients in contrast to eight cases of post-ERCP pancreatitis ($P < 0.01$) in the conventional group. The study of Lee *et al*[1] also supports the use of a guide wire. When conventional cannulation with a contrast injection was compared with wire-guided cannulation, the rate of post-ERCP pancreatitis was higher in the conventional group, 11.3%, than in the wire-guided group ($P = 0.001$)[1]. It is thought that the guide-wire approach is gentler than using a catheter alone and also lessens the risk of accidental injection of the contrast medium into the main pancreatic duct or the papilla itself, thereby reducing pancreatic injury caused by chemicals or pressure.

Table 2 Success and pancreatitis rates with cannulation techniques

	%	Ref.
Primary success in cannulation		
Standard catheter	54 to 67	[3,30]
Standard catheter with guide wire	81	[3]
Sphincterotome	78 to 84	[4,29]
Sphincterotome with guide wire	97 to 99	[26,30]
Success in difficult cannulation after primary failure with standard method		
Persistence	73 to 75	[2,49]
Needle knife	67 to 91	[2,6,9,34,37]
Erlangen knife	78 to 100	[32,50]
Pancreatic sphincterotomy	91 to 100	[10,12,13,22,40,41]
Pancreatic stent	97 to 100	[28,47]
Pancreatic guide wire	73 to 93	[5,8]
Pancreatitis rate after difficult cannulation		
Persistence	2-4	[2,49]
Needle knife	1-11	[2,6,9,34,37]
Erlangen knife	3-7	[32,50]
Pancreatic sphincterotomy	0-12	[10,12,13,22,40,41]
Pancreatic stent	5-7	[28,47]
Pancreatic guide wire	0-2	[5,8]

Randomized controlled trials were used in literature 2, 3, 5, 10, 26, 28, 29, 30 and 49.

Pancreatic duct stents have been used to prevent post-ERCP pancreatitis in several studies[27]. In a prospective study in Milwaukee, only patients at a high risk of pancreatitis were recruited into the study. Patients who were considered to be at high risk were those who had sphincter of Oddi manometry, endoscopic sphincterotomy or difficult cannulation. Difficult cannulation was defined as needing more than 30 min manipulation time. A group of 76 patients was randomised into two groups: one group received a pancreatic stent (n = 36) and the other did not (n = 38). The results favoured pancreatic stenting, as 28% of the patients without a stent developed pancreatitis versus only 5% in the stented group ($P < 0.05$)[11]. Inserting a pancreatic stent after biliary sphincterotomy in patients with sphincter of Oddi dysfunction (SOD) had a similar protective effect. In a randomised study of 80 patients, the risk of pancreatitis decreased from 26% to 7% ($P = 0.03$)[28].

PRIMARY CANNULATION RESULTS

Standard catheters as primary tools only have success rates from 54% to 67%[3,4,29,30]. This translates into failures or difficult cannulations in 46% to 33% of cases. Bendable catheters have been shown to perform only slightly better[4]. When the standard catheter is used with a guide wire, cannulation failures drop to less than 19%[14,31].

As an example, in a study in Greece a standard catheter and a catheter combined with a hydrophilic guide wire were compared when trying to get access into the common bile duct. If the cannulation did not succeed in 10 min, a further 10-min attempt was tried using the guide wire. The primary success rate with the standard catheter was 54% versus 81% with the hydrophilic guide wire ($P < 0.001$). After crossover, the cannulation rates were equal (84%) for the two groups[3].

The use of a sphincterotome as the initial device is nearly as effective as using a catheter with a guide wire. The reported primary failures for sphincterotomes have been between 24% and 16%[1,4,29]. When the sphincterotome is used with a guide wire, primary cannulation failures tend to be less than 10%[2] an one study reported a failure rate of just 3%. This report of Cortas *et al*[30] of a small prospective trial provides a good example of the use and efficacy of a standard catheter versus a wire-guided sphincterotome. Failure was defined as an inability to achieve opacification or deep cannulation after 15 attempts with the initial catheter. Eighteen patients were randomised to the standard catheter group and 29 patients to the standard/wire-guided sphincterotome group. Initial common bile duct cannulation was successful in 67% and 97%, respectively. The mean number of attempts was 12 and 3 ($P = 0.0001$) and the mean time 14 min and 3 min ($P = 0.0001$), respectively.

An similarly positive result with a sphincterotome and guide wire was reported by Karamanolis *et al*. In their study, the primary tool was a standard ERCP catheter with or without a guide wire, with a primary success rate of 82%. The cannulation was tried until there were five unsuccessful attempts with the standard catheter and 10 more attempts with the catheter and guide wire[14]. Obviously the primary result represents wire-guided cannulation and is well in line with other reports[3,31]. When the patients with difficult cannulation were crossed over to the sphincterotome and guide-wire procedure, deep bile duct cannulation was achieved in 83%, amounting to an overall success rate of 97% before precuts. In this study, 10 attempts were allowed for the sphincterotome and guide wire combination. There was no significant difference in post-ERCP pancreatitis in the groups (6% and 7%, respectively) (Table 2).

SOLUTIONS FOR OVERCOMING DIFFICULT CANNULATION

With an effective primary cannulation technique, the rate of difficult cannulations remains around 10% of intact papillae, depending on how the operator defines difficult cannulation. Following identification of a difficult canulation comes the choice of how to proceed. Possibilities include changing the catheter or the operator, or to apply more aggressive methods, keeping in mind the increasing risk of complications. Among possible further steps, needle-knife precut sphincterotomy, papillary roof excision, transpancreatic sphincterotomy, transpancreatic stenting, double wire technique, persistence, papillectomy and special knifes can be used. Of course, if endoscopic methods fail, the transhepatic route can be used directly without an endoscopist or the rendezvous technique can be applied, depending on the problem.

Until now, the most commonly used solution in a difficult situation has been the use of a needle knife to perform an access papillotomy. More recently, however, transpancreatic sphincterotomy is beginning to gain ground, too.

NEEDLE-KNIFE PRECUT

The precut rate varies from zero to as much as 38%-50% of all biliary cannulation attempts[32,33]. Precut sphincterotomy with a needle knife is performed either by avoiding the papillary orifice and opening the mucosa above it[34], usually called fistulotomy, or by a technique where the incision starts from the papillary orifice. In a retrospective study by Abu-Hamda et al., these methods did not differ in success (90%-96%) or complication (2%-13%) rates[35]. Although the precut papillotomy may improve the cannulation success rate, prospective studies have suggested that it is an independent risk factor for post-ERCP complications[18,36]. In one study, however, the needle-knife precut did not increase the risk of complications[19]. In general, precut sphincterotomy has a cannulation rate of 92%-93% and a complication rate of 10%-11%[34,37] although a complication rate of as much as 30% has been reported[38].

If the biliary cannulation attempt was unsuccessful after 20 min, it was defined as being difficult by Fukatsu et al. Standard cannulae failed in 16% of cases. Thereafter a needle-knife papillotomy was performed. The needle-knife sphincterotomy was successful in 88% of cases during the first session[9]. In a study by Laasch et al. involving 312 patients, a needle-knife precut was performed in 23 (7.4%) patients when cannulation by other means had failed. Deep access into the bile duct during the first ERCP session was achieved in 20 patients (87%) with an overall success rate of 97%[4].

In another study, early precutting with a needle knife in 70 out of 346 patients (20%) had an initial success rate of 83%, amounting to a total initial success rate of 97%, and 99% after two sessions. Two different precutting techniques were used, with no difference in complications between the groups[6].

PANCREATIC SPHINCTEROTOMY

Instead of performing a precut with a needle knife after a failed attempt to reach the biliary duct, one alternative is to perform a pancreatic sphincterotomy, which was first described in 1985 for pancreatic procedures[39]. Ten years later the method was reported as a means to access the common bile duct[40]. A sphincterotomy over the guide wire in the pancreatic duct helps to cannulate the biliary orifice as the cut either opens the biliary duct or runs along the side of the duct, thus exposing the duct's anatomy. In over half of cases, the lumen of the common bile duct becomes visible and can be cannulated with either a catheter or a sphincterotome with or without a guide wire. If not, an oblique cut with the needle knife exposes the common bile duct[22]. The advantage of this transpancreatic sphincterotomy is that the depth and location of the incision in relation to the bile duct is more controlled than with the needle-knife precut.

The rate of pancreatic sphincterotomy tends to differ considerably. While Goff reported an incidence of pancreatic sphincterotomy as high as 36%, Kahaleh *et al* had a rate of 5% for pancreatic sphincterotomy in difficult biliary cannulation[13,41]. In the prospective study by Kahaleh *et al*, the primary success rate with pancreatic sphincterotomy was 85% and, when combined with the needle-knife technique, it rose to 95%. The complication rate was 12%. There was no difference in the pancreatitis rate between conventional biliary sphincterotomy and pancreatic precut.

When pancreatic sphincterotomy was compared with needle-knife sphincterotomy, the pancreatic sphincterotomy had a 100% success rate for biliary cannulation compared with 77% in needle-knife precutting. Complication rates were 4% versus 18%[10]. Goff reported a complication rate of 2% after standard sphincterotomy and only 2% for the transpancreatic approach. It is remarkable that there were no cases of post-ERCP pancreatitis in the latter group[41].

In a retrospective study, the complication rate associated with the pancreatic sphincterotomy technique was equal to the overall ERCP complication rate[22]. However, in patients with primary sclerosing cholangitis the rate of post-ERCP pancreatitis was 25%, similar to patients with SOD in other studies, when pancreatic sphincterotomy was performed[22,28].

Even where conventional biliary cannulation and needle-knife precutting failed to achieve access to the bile duct, the pancreatic sphincterotomy was successful in 95% of the cases and the complication rate was 11%, indicating that this technique is safe and effective[12].

In an analysis of ERCP-related complications, needle-knife precutting, but not pancreatic sphincterotomy, was identified as a risk factor for overall complications [odds ratio (OR) 2.70] and for post-ERCP pancreatitis (OR 4.34)[40]. These authors suggest that the risk after transpancreatic precut might be lower than after precutting with a needle knife.

The question of inserting a pancreatic stent after pancreatic sphincterotomy has been addressed in two reports. Esber *et al*[42] found no difference between using and not using a stent. In the study of Kahaleh *et al* the use of a prophylactic pancreatic stent had an adverse rather than a protective effect. The rate of pancreatitis was 14% versus 6%, in favour of not using the pancreatic stent[13].

The question of possible long-term sequalae after pancreatic sphincterotomy has been raised but still remains unanswered[43]. There are few, mostly anecdotal, reports of papillary stenosis causing relapsing pancreatitis. These cases, however, have occurred after biliary sphincterotomy[44-46]. Whether or not papillary stenosis is an

important clinical problem after the transpancreatic approach still awaits clarification through substantial follow-up studies on the subject.

OTHER SOLUTIONS

Inserting a pancreatic stent to facilitate biliary cannulation has been used with success either in difficult cannulation or in the case of a diverticulum. Goldberg et al. reported on a series of 39 patients, with an initial success rate of 90% and final success in 38 patients (97%). Only 5% developed mild pancreatitis. A standard sphincterotome was used for cannulation after inserting the pancreatic stent. Fifty-nine per cent of the patients required a precut sphincterotomy to gain access to the biliary duct[47]. The diverticulum problem was dealt with by Fogel *et al* by inserting a pancreatic stent and then gaining access to the bile duct with a needle knife. Across two sessions, the procedure was successful in 88% of the patients although two out of eight patients developed post-ERCP pancreatitis[48].

Persistence may pay off. In a randomised study in Toronto, patients who had difficult cannulation were randomised either to precut sphincterotomy by a needle knife over the roof of the papilla or to persistent cannulation with a non-wire-guided papillotome. In this study, the difficult cannulation was defined as a failed cannulation after 12 min. The difficult cannulation group consisted of 62 patients (11%) out of a total of 642. They were assigned to the precut arm (n = 32) or to the persistence arm (n = 30). After randomisation, primary success was defined as cannulation of the biliary duct within 15 min. Precut and persistence were equally effective with regard to success (75% *vs* 73%) and complication (4% *vs* 9%) rates. The primary success rate after 15 min was 98% and after the full ERCP session the rate rose to 99.5%[49]. A similar result for persistence was obtained by a Shanghai group. If the biliary cannulation failed within 10 min or the guide wire entered the pancreatic duct three times, the patients were randomised either to needle-knife papillotomy or to persistent cannulation with a double-lumen sphincterotome. Out of a total of 948 patients, there were 91 (9.5%) patients with difficult cannulation, of which 43 were randomised to needle-knife sphincterotomy and 48 to persistence. With the needle knife, the success rate was 91% and the mean cannulation time was 5.5 min, with 9% complications. Persistence was successful in 75%, with a mean cannulation time of 10 min and 15% complications. The only statistically significant difference between the groups was the cannulation time in favour of needle-knife sphincterotomy[2].

The Erlangen precut papillotome is an alternative to the needle-knife technique for performing a precut papillotomy. The tip of the instrument enters the papillary lumen and the roof of the papilla is opened. With this method, the final deep biliary cannulation rate in cases with problematic cannulation was 98%, and complications occurred at a similar rate (8.3%) to that in non-precut patients (7.1%)[32,50].

Endoscopic papillectomy has been proposed as an approach to difficult cannulation[51]. In a small study of 10 patients with failed previous cannulation, all had protuberant ampullae. After ampullectomy, successful biliary and pancreatic cannulation was achieved in all 10 cases. There were no cases of pancreatitis although no pancreatic stent was used. One patient, however, had significant bleeding afterwards. The more common indication for papillectomy is removal of an adenoma. In this situation, the risk for pancreatitis is higher if no pancreatic stent is inserted[52]. Obviously, in the majority of cases of difficult cannulation this method is not feasible. Most papillae are small, flat or even endophytic and have to be accessed by different means.

A pancreatic guide wire has been used to help biliary cannulation in difficult cases. The method was used on 113 patients, with a success rate of 73%[8]. The patients represented only 2.9% of the total, and were considered to be the most difficult population. Post-ERCP pancreatitis occurred in 12%. In this study, inserting a pancreatic stent was a protective factor. It has to be noted, however, that no pancreatic sphincterotomy was performed[8]. A randomised study with 53 patients from Japan found that a pancreatic guide wire gave a higher success rate of 93% compared with a conventional catheter (58%)[5].

When conventional ERCP methods fail, EUS guided biliary access may still be an option, although it is rarely used at present[53,54].

CONCLUSION

Cannulation is usually performed with a catheter or a sphincterotome. Only in special cases of difficult cannulation due to anatomy, diverticula, lack of space or bulky papilla are extraordinary measures necessary[7,51].

The use of needle-knife precutting still remains the primary choice of most endoscopists in difficult cannulations. Nevertheless, studies show that there is a slightly higher complication rate connected with the use of a needle knife when compared with the transpancreatic approach. In addition, pancreatic sphincterotomy has a better success rate in randomised studies. When used as the first choice in difficult situations, the difference in favour of pancreatic precutting is even greater.

Cannulation with a guide wire is, in light of published studies, faster and safer than without one, be it with a catheter or a sphincterotome. A papillotome has the advantage, especially in the case of a rotatable sphincterotome, that its tip can be better adjusted to the papilla and it can be used for manipulation in difficult cases. A guide wire definitely improves accuracy and selection of the desired duct without a contrast injection is possible. On the other hand, a tendency towards the use of a sphincterotome with a guide wire is increasing as purely diagnostic ERCPs are rarely needed any more. A sphincterotome is nearly always necessary as a papillotomy

is the next step in paving the way for further procedures. The same applies to the guide wire in securing access. With a wire-guided sphincterotome, the primary cannulation success rises to around 90%. With a rotatable sphincterotome even the most difficult situations, such as problems with diverticula, are easier to handle.However, in many cases the guide wire enters the pancreatic duct. The location is usually clearly distinguishable without contrast injection under fluoroscopy. If this happens several times, an easy solution is to continue to perform a pancreatic sphincterotomy instead of resorting to a needle knife. This method has proven to be a nearly fail-safe procedure in accessing the common bile duct. If necessary, a further precut with a needle knife accomplishes the task. In less than half of pancreatic sphincterotomy cases, an additional needle-knife cut is necessary to access the biliary duct. An extra needle-knife cut does not increase the complication rate[22].

Currently, there is no well-founded reason to use pancreatic stents in connection with pancreatic sphincterotomy. The situation is different when treating patients with sphincter of Oddi dysfunction or papillary adenomas. There, the protective effect of the pancreatic stent has been well proven.

With a proper selection of tools, cannulation is usually a fast procedure. Much more time is spent on the actual treatment. The time necessary for the primary cannulation in a regular case with a wire-guided sphincterotome is less than 5 min, and requires only a couple of attempts[30]. With this in mind, a difficult cannulation could be defined as anything that takes more than 5 min and/or five attempts on the papilla. A more flexible view of the definition would be 10 min and/or 10 attempts, as has been most often used in recent reports. For the time being, the definition in prospective studies has to include the time frame, number of attempts or injections and especially the tools used. The rate of primary failures depends mainly on tool selection. The reported success rates vary from 52% to 97%. However, irrespective of secondary tool selection in difficult cases, the final success rate can be expected to be well over 96% regardless of the primary tool. According to the best reports, a nearly total success rate has been achieved[1,3,49].

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CASE REPORT

Bone formation in a rectal inflammatory polyp

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Abstract

Heterotopic bone formation (osseous metaplasia) is rarely detected in the gastrointestinal tract. Most of reported cases are associated with malignant lesions. We herein report a case of osseous metaplasia in a rectal inflammatory polyp and a review of the literature on suggested mechanisms for its aetiology. A 39-year-old man visited our hospital with a chief complaint of melena. Total colonoscopy revealed a slightly reddish subpedunculated polyp, about 12 mm in diameter, in the lower rectum. Endoscopic resection was performed. Histologically, several foci of heterotopic bone formation were found. From the review of the literature, all of the polyps described were larger than 10mm in diameter, 55.6% showed inflammatory changes, and 62.5% were detected in the rectum. Osteogenic stimulation was considered to be a result of the inflammatory process. As our inflammatory polyp was located in the rectum, the pathogenesis could be a reactive change stimulated by the repeated local trauma, or be on a peculiar characteristic of the rectal mucosa itself.

Key words: Osseous metaplasia; Rectal polyp; Inflammatory polyp; Rectum; Inflammatory process

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INTRODUCTION

Heterotopic bone formation (osseous metaplasia) is rarely detected in the gastrointestinal tract. Most of reported cases are associated with malignant lesions[1,2]. We herein report a case of osseous metaplasia in a rectal inflammatory polyp and review the literature on suggested mechanisms for its aetiology.

CASE PRESENTATION

A 39-year-old man visited our hospital with a chief complaint of melena. Total colonoscopy was carried out on the cecum uneventfully, and nothing but a slightly reddish subpedunculated polyp (Paris classification Isp), about 12 mm in diameter, was detected in the lower rectum (Figure 1A). The surface of the polyp was covered with whitish exudate, which suggested inflammatory change. Magnifying observation with dye-spraying using 0.4% indigo carmine revealed a type I pit pattern according to the Kudo's classification, which indicated that this polyp was non-neoplastic (Figure 1B). Therefore, an endoscopic diagnosis of an inflammatory polyp was established. However, endoscopic resection

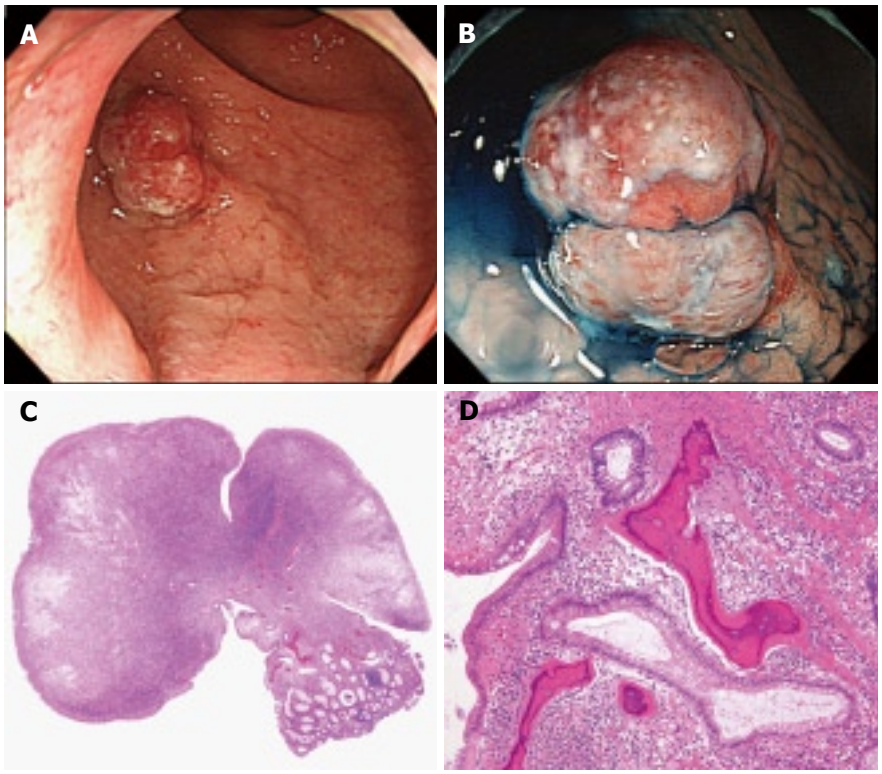

Figure 1 Subpedunculated polyp in the lower rectum. A: Colonoscopy revealed a slightly reddish subpedunculated polyp, about 12 mm in diameter, in the lower rectum. The surface of the polyp was covered with whitish exudate, which suggested inflammatory change; B: Magnifying observation with dye-spraying using 0.4% indigo carmine revealed a type Ⅰ pit pattern according to the Kudo's classification; C: Histologically, the surface of the resected specimen was mostly covered by inflammatory exudate and partly by regenerating epithelium; D: Several foci of heterotopic bone formation were also found on histology.

Table 1 Summary of reported cases of osseous metaplasia in benign colorectal polyps

Case	Author	Year	Age	Gender	Size (mm)	Location	Histology	Inflammation	Mucin deposition	Ref.
1	Sperling	1981	25	M	10	Rectum	Inflammatory polyp	+	+	[3]
2	Castelli	1992	22	F	10	Rectum	Inflammatory polyp	+	-	[4]
3	Groisman	1994	67	M	18	Rectum	Tubulovillous adenoma	-	-	[5]
4	Groisman	1994	3	F	20	Rectum	Juvenile polyp	+	+	[5]
5	Cavazza	1996	NI	NI	NI	NI	Tubulovillous adenoma	NI	NI	[6]
6	McPherson	1999	73	M	20	Cecum	Tubulovillous adenoma	-	-	[7]
7	Rothstein	2000	NI	NI	25	Sigmoid colon	Tubular adenoma	-	-	[8]
8	Al-daraji	2005	85	F	15	Sigmoid colon	Tubular adenoma	-	-	[9]
9	White	2008	63	F	NI	Transverse colon	Tubular adenoma	+	-	[10]
10	Present case	2009	39	M	12	Rectum	Inflammatory polyp	+	-	Present case

NI: Indicates not informative.

was performed for histological evaluation, as the polyp was larger than 10 mm. The polyp was completely removed *en bloc* with EMR (the lift and cut technique) without complication. Histologically, the surface of the resected specimen was mostly covered by inflammatory exudate and partly by regenerating epithelium (Figure 1C). Moreover, the polyp was composed of inflammatory granulation tissues with numerous capillaries and marked acute and chronic inflammatory cells infiltration. Several foci of heterotopic bone formation were also found on histology (Figure 1D). A pathological diagnosis of a rectal inflammatory polyp with osseous metaplasia was finally made.

DISCUSSION

Stromal ossification often occurs in gastrointestinal cancers from the stomach to the rectum and appears to result from tumor production of bone morphogenic protein[2]. Heterotopic ossification in benign colon polyps has, however, been documented only rarely. To the best of our knowledge, there are only nine cases other than ours which have been reported[3-10]. We have reviewed and summarized the related literature on osseous metaplasia in benign colon polyps (Table 1). The patients comprised 4 men and 4 women, plus two who gender was not described, with a mean age of 47 yr (range: 3 to 85 y). All of the polyps were larger than 10mm in diameter, and the mean size was 16.3 mm (range: 10-25 mm). Histologically, 6 lesions were neoplastic (3 tubular adenomas and 3 tubulovillous adenomas), whilst the remaining 4 lesions were non-neoplastic (3 inflammatory polyps and a juvenile polyp). In addition, 5 out of 9 lesions (55.6%) showed inflammatory changes, and 2 out of 9 lesions (22.2%) demonstrated mucindeposition, whilst information was lacking for one case. The most commonly involved site

was rectum where 5 out of 8 polyps (62.5%) were detected.

Histologically, necrosis, inflammation, pre-existing calcification, increased vascularity, and extracellular mucindeposition were reported to be associated with heterotopic bone formation in tumors[2]. Various mechanisms have been suggested although the pathogenesis of osseous metaplasia still remains unknown. The tumor cells may secrete an unknown substance that stimulates bone formation. The largest case review (52 cases) of osseous metaplasia in the gastrointestinal tract (excluding liver and pancreas) was by Ansari *et al*[11] in 1992. In this review, the mean subject age was 55 years, and the diagnosis in 47 of the 52 cases was that of an adenocarcinoma. The majority of cases were documented in the colon, the most common site being the rectum (21/52 cases). Osseous metaplasia seemed to occur more frequently in the primary tumor. Histologically, both benign and malignant lesions with osseous metaplasia were commonly seen with the presence of mucin production and extravasation. On the other hand, benign lesions with osseous metaplasia were often seen with a histological background of active chronic inflammation and/or ulceration[2].

From the review of the literature, all of the polyps were larger than 10 mm in diameter, 55.6% showed inflammatory changes, and 62.5% were detected in the rectum. Persistent inflammation may also play a role in osseous metaplasia in benign colonic lesions. Osteogenic stimulation was considered to be a result of the inflammatory process. Our inflammatory polyp was located in the rectum, and composed of inflammatory granulation tissues with numerous capillaries and marked acute and chronic inflammatory cells infiltration. The pathogenesis could, therefore, be a reactive change stimulated by the repeated local trauma, or be a peculiar characteristic of the rectal mucosa itself. Clinically, the presence of the metaplastic bone seems to be innocent.

In conclusion, we have reported an extremely rare case of heterotopic bone formation in a rectal inflammatory polyp where persistent inflammation may also play a role in the pathogenesis of osseous metaplasia.

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World J Gastrointest Endosc 2010 March 16; 2(3): I
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Meetings

Events Calendar 2010

January 25-26
Tamilnadu, India
International Conference on Medical Negligence and Litigation in Medical Practice

January 25-29
Waikoloa, HI, United States
Selected Topics in Internal Medicine

January 26-27
Dubai, United Arab Emirates
2nd Middle East Gastroenterology Conference

February 11-13
Fort Lauderdale, FL, United States
21th Annual International Colorectal Disease Symposium

February 26-28
Carolina, United States
First Symposium of GI Oncology at The Caribbean

March 05-07
Peshawar, Pakistan
26th Pakistan Society of Gastroenterology & Endoscopy Meeting

March 12-14
Bhubaneswar, India
18th Annual Meeting of Indian National Association for Study of the Liver

March 25-28
Beijing, China
The 20th Conference of the Asian Pacific Association for the Study of the Liver

March 27-28
San Diego, California, United States
25th Annual New Treatments in Chronic Liver Disease

April 07-09
Dubai, United Arab Emirates
The 6th Emirates Gastroenterology and Hepatology Conference, EGHC 2010

April 14-17
Landover, Maryland, United States
12th World Congress of Endoscopic Surgery

April 14-18
Vienna, Austria
The International Liver Congress™ 2010

April 28-May 01
Dubrovnik, Croatia
3rd Central European Congress of surgery and the 5th Croatian Congress of Surgery

May 01-05
New Orleans, LA, United States
Digestive Disease Week Annual Meeting

May 15-19
Minneapolis, MN, United States
American Society of Colon and Rectal Surgeons Annual Meeting

June 04-06
Chicago, IL, United States
American Society of Clinical Oncologists Annual Meeting

June 16-19
Hong Kong, China
ILTS: International Liver Transplantation Society ILTS Annual International Congress

June 20-23
Mannheim, Germany
16th World Congress for Bronchoesophagology-WCBE

August 28-31
Boston, Massachusetts, United States
10th OESO World Congress on Diseases of the Oesophagus 2010

September 10-12
Montreal, Canada
International Liver Association's Fourth Annual Conference

September 11-12
La Jolla, CA, United States
New Advances in Inflammatory Bowel Disease

September 16-18
Prague, Czech Republic
Prague Hepatology Meeting 2010

September 23-26
Prague, Czech Republic
The 1st World Congress on Controversies in Gastroenterology & Liver Diseases

October 07-09
Belgrade, Serbia
The 7th Biannual International Symposium of Society of Coloproctology

October 15-20
San Antonio, TX, United States
ACG 2010: American College of Gastroenterology Annual Scienitfic Meeting

October 23-27
Barcelona, Spain
18th United European Gastroenterology Week

October 29-November 02
Boston, Massachusetts, United States
The Liver Meeting® 2010--AASLD's 61st Annual Meeting

November 13-14
San Francisco, CA, United States
Case-Based Approach to the Management of Inflammatory Bowel Disease

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Instructions to authors

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tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

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

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

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

Chapter in a book (list all authors)

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

Author(s) and editor(s)

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

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

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

Patent (list all authors)

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

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Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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