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EDITORIAL

Management of early asymptomatic gastrointestinal stromal tumors of the stomach

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Abstract

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the digestive tract. Approximately two thirds of clinically manifest tumors occur in the stomach, nearly one third in the small bowel, and the rest in the colorectal region with a few cases in the esophagus. GIST originate within the smooth muscle layer in the wall of the tubular gastrointestinal tract and grow mostly toward the serosa, far less often toward the mucosa. In the latter case, ulceration may develop and can cause gastrointestinal bleeding as the cardinal symptom. However, most GIST of the stomach are asymptomatic. They are increasingly detected incidentally as small intramural or submucosal tumors during endoscopy and particularly during endoscopic ultrasound. Epidemiological and molecular genetic findings suggest that early asymptomatic GIST of the stomach (< 1 cm) show self-limiting tumorigenesis. Thus, early (< 1 cm) asymptomatic gastric GIST (synonym: micro-GIST) are found in 20%-30% of the elderly. The mostly elderly people with early gastric GIST have an excellent GIST-specific prognosis. Patients with early GIST of the stomach can therefore be managed by endoscopic surveillance.

Key words: Mirco-gastrointestinal stromal tumors; Gastrointestinal stromal tumor; Gastric; Neoplasia; Cancer; Endoscopy; Endoscopic ultrasound

Core tip: Small gastric gastrointestinal stromal tumors (GIST) are by far the commonest neoplasias of the stomach. Thus, early gastric GIST of less than 1 cm in size are found in 20%-30% of the elderly. The natural disease-specific prognosis of early gastric GIST (< 1 cm), also called micro-GIST, is excellent in the mostly elderly patients. Micro-GIST of the stomach appear to have a self-limiting tumorigenesis. Local endoscopic or surgical resection of early asymptomatic GIST (< 1 cm) of the stomach is in general not indicated in the elderly. Instead endoscopic surveillance is advised.

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INTRODUCTION

Gastrointestinal stromal tumors (GIST) originate from mesenchymal cells, *i.e.*, the socalled interstitial cells of Cajal that act as pacemakers, or from a common precursor cell along the intestine. Approximately 50%-70% of clinically manifest tumors arise in the stomach, 20%-30% in the small bowel, 5%-15% in the large bowel and less than 5% in the esophagus or other locations. The mean age

at diagnosis is between 66 and 69 years for both women and men. About 3% of clinically manifest GIST are diagnosed before the age of 21 years. Their occurrence is predominantly sporadic[1]. There may be a connection with hereditary diseases in a small percentage of cases (neurofibromatosis type 1, Carney triad, familial GIST and mastocytosis).

Clinically manifest GIST are rare with an annual incidence rate of 10 to 20 cases per million population[2]. Much more common, on the other hand, are early (up to 1 cm large) asymptomatic gastric GIST, also called micro-GIST, which are found in 20%-30% of the elderly[3-5]. The striking discrepancy between the incidence of GIST in autopsy stomachs or gastrectomy specimens and the incidence of clinically manifest GIST suggests that early asymptomatic GIST of the stomach are precursor lesions from which clinically manifest GIST arise only in exceptional cases. Thus the characteristics of early asymptomatic GIST of the stomach will be discussed here with reference to clinical management.

SYMPTOMS AND DIAGNOSIS

The vast majority of early gastric GIST are asymptomatic. Patients with symptomatic gastric GIST, which are usually larger than 2-3 cm, most commonly present with gastrointestinal bleeding, anemia, epigastric pain and sometimes palpable resistance, vomiting, and weight loss.

GIST metastasize mainly to the liver and peritoneum. Lung and bone metastases are unusual, and lymph node metastases are rare. Laboratory examinations are of no diagnostic value. Metastases can be detected by ultrasound and CT scans; the latter may be optionally combined with positron emission tomography (FDGPET/CT)[6].

ENDOSCOPY

Gastroscopy is the standard procedure for diagnosing GIST of the stomach. Endoscopy detects the mostly intramural tumors and also enables endoscopic ultrasound (EUS)-guided acquisition of cytological and histological samples. The latter is imperative for a definitive diagnosis. In contrast to histology, cytology does not allow for determination of the mitotic rate. In emergency situations where urgent surgery is indicated, the clinically suspected diagnosis of GIST is verified postoperatively by histological evaluation of the resected tumor specimen.

Typical endoscopic findings in patients with early gastric GIST are shown in Figure 1. Early asymptomatic GISTs of the stomach are mostly detected incidentally during gastroscopy as submucosal protrusions < 1 cm in diameter. Due to their submucosal or intramural location, however, they usually cannot be verified histologically by routine biopsies of the superficial normal mucosa. Endoscopic submucosal resection (ESMR) might be a procedure for diagnosing the very few, early gastric GIST that are confined to the mucosa and submucosa[7]. No reports are available on ESMR or endoscopic mucosal resection (EMR) for early gastric GIST[8]. R0 resection of the more common gastric GIST that arise from the muscularis propria cannot be achieved using traditional endoscopic techniques. However, a lot of them can be completely en bloc resected by endoscopic submucosal dissection in expert hands[9]. (Laparoscopic) Surgical resection is the method of choice for larger GIST.

EUS AND EUS-FNA

EUS plays a decisive role in the diagnosis, the measurement of size, the assessment of local infiltration, and clinical management of submucosal or intramural lesions of the stomach. It reliably distinguishes mucosal lesions from a submucosal mass or extramural compression. EUS is often able to correctly identify the type of lesion based on its echo features, its assignment to a specific wall layer or its location outside the stomach.

EUS examinations can be performed with a radial scanner (360°) or a linear echoendoscope. Filling the stomach with water optimizes acoustic coupling of the probe to the stomach wall. Gastric GIST typically arise from the fourth echo layer of the stomach wall (muscularis propria), rarely also from the submucosa (third echo layer). They are usually visualized as oval-to-elliptical hypoechoic lesions with a smooth border. Large GIST often show a large central anechoic blood vessel or hyperechoic air bubbles in the case of central ulceration. On EUS images, large GIST can appear inhomogeneous with hypo- and hyperechoic parts. GIST characteristically lack paragastric lymph node metastases; this too can be clearly demonstrated with EUS.

In the acquisition of cytological and histological samples, EUS-guided biopsy of the submucosal or intramural GIST plays a decisive role. The definitive cytological and/or histological verification of larger gastric GIST is currently achieved in 50%-70% of EUS-guided fine-needle aspiration (FNA) or EUS-guided Trucut punch biopsies[10-15]. The histological diagnosis of GIST requires immunohistochemical detection of CD117 and particularly in CD117-negative tumors of DOG1 with the corresponding histomorphological findings. Most early GIST of the stomach can be followed-up by endoscopic examinations (EUS) even without initial histological confirmation.

PATHOLOGY, METASTATIC RISK AND PROGNOSIS

The diagnosis of GIST first came into existence in 1998 when the CD117 antigen was identified as being almost invariably expressed by GIST in over 90% of the cases; in contrast, leiomyomas, leiomyosarcomas and other spindle-cell gastrointestinal tumors are typically CD117-negative. CD117 antigen is the type Ⅲ transmembrane receptor tyrosine kinase KIT, a KIT proto-oncogene product[1]. Approximately 95% of GIST in adulthood

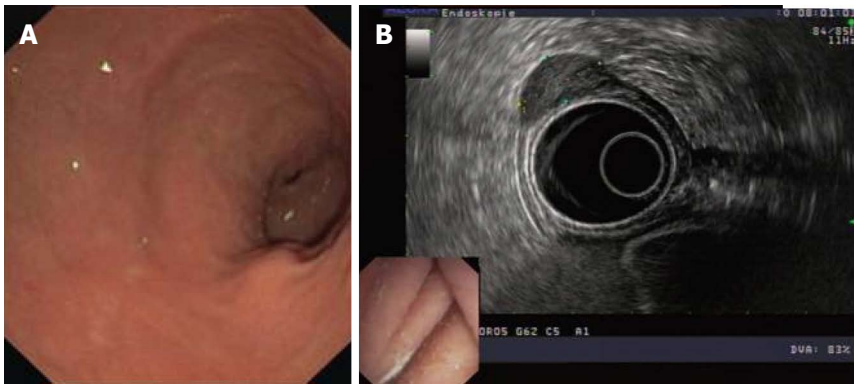

Figure 1 Typical endoscopic features of an early gastrointestinal stromal tumors of the stomach. A: Endoscopic image of an early GIST of the stomach; B: Endosonographic image of an early GIST of the stomach. Modified from reference [33]. GIST: Gastrointestinal stromal tumors.

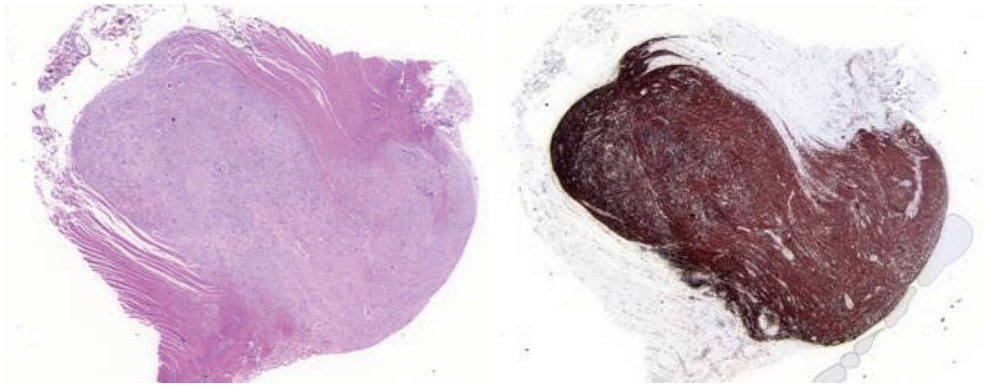

Figure 2 Histological images of an early gastrointestinal stromal tumors of the stomach. A: Gastric GIST of the muscularis propria displaying spindle cell type (HE stain); 2B: GIST of the muscularis propria displaying spindle cell type (CD 34 stain). Modified from reference [33]. GIST: Gastrointestinal stromal tumors.

overexpress KIT. Nearly 80% of GIST show *KIT* gene mutations that lead to constitutive activation of the KIT receptor. More than 60% of the *KIT* activating mutations occur in exon 11. About 10% of the cases have mutations in exon 9, much more rarely (< 2%) in exon 13 or 17. Instead of *KIT* mutations, about 15% of all GIST have analogous mutations in the plateletderived growth factor receptor alpha (*PDGFRA*) gene; here they cluster in exon 18, more rarely in exon 12 or 14. They are preferentially detected in the stomach but hardly ever in other gastrointestinal locations. The tumors often show an epithelioid histomorphological phenotype[16,17].

Much attention is nowadays payed to the diagnostic marker DOG1, a protein with 8 transmembrane domains that constitutes a calcium-regulated chloride ion channel. DOG1 probably has even higher sensitivity for GIST than CD117. Moreover, the marker shows high sensitivity for CD117-negative GIST[18,19]. In non-GIST, on the other hand, DOG1 positivity has only been observed in a few isolated cases. GIST express CD34 in 70%-80% of the cases, whereas a KIT expression is found in more than 90% of cases. Immunohistochemical stains for CD117, DOG1 and CD34 are now routinely used in the identification and diagnosis of GIST (Figure 2). Antibodies against smooth muscle actin, desmin and S100 enable to distinguish GIST from leiomyomas or schwannomas.

According to Miettinen und Lasota, the postoperative prognosis of patients with gastric GIST can be predicted based on the following clinicopathological parameters: tumor location, tumor size and mitotic rate/5 mm^2 (Table 1). The original population used 50 HPFs to evaluate this area but stated that with newer microscopes bearing larger field diameters an area of 5 mm^2 would be appropriate. Accordingly, the ESMO guidelines from 2012 recommend to evaluate 5 mm^2 instead of 50 HPFs[20-22]. Thus, tumors with a maximum diameter of 2 cm and low proliferative activity have a negligible risk of progression.

EARLY GIST (MICRO-GIST)

Early GIST of the stomach (< 1 cm) differ clinically and pathologically from clinically relevant tumors in that they have a markedly lower proliferation rate. They also occur more often as hypocellular lesions composed of spindle cells and frequently show marked sclerosis. Early gastric GIST (synonym: micro-GIST) exhibit distinctive molecular genetic characteristics: the incidence of *KIT*/*PDGFRA* mutations and particularly *KIT* exon 11 mutations is significantly lower in early than in clinically manifest GIST. There is a high frequency of unique mutations that have thus far not been found in clinically relevant GIST. A large Italian study identified five new mutations,

Table 1 Risk of progression for gastric gastrointestinal stromal tumors according to Miettinen

Tumor parameters		Risk of tumor progression
Mitosis rate	Size	
≤ 5/5 mm^2	≤ 2 cm	0%
≤ 5/5 mm^2	> 2-5 cm	1.90%
≤ 5/5 mm^2	> 5-10 cm	3.60%
≤ 5/5 mm^2	> 10 cm	12%
> 5/5 mm^2	≤ 2 cm	ND
> 5/5 mm^2	> 2-5 cm	16%
> 5/5 mm^2	> 5-10 cm	55%
> 5/5 mm^2	> 10 cm	86%

According to Miettinen *et al*[20-22]. ND: No data.

three in KIT (p.Phe506Leu, p.Ser692Leu, p.Glu695Lys) and two in PDGFRA (p.Ser847X, p.Ser667Pro), as well as four double mutations[5]. These mutations apparently only cause low proliferative activity in GIST. There are also mutations consistent with clinically relevant GIST[23].

Prognosis of patients with early GIST of the stomach

Clinical progression of early gastric GIST (< 1 cm) has not yet been described in the world literature. Thus early gastric GIST generally show benign behavior irrespective of the mitotic rate and exhibit distinctive histopathological and molecular biological characteristics[5]. The GIST-specific prognosis of patients with early gastric GIST is excellent.

CLINICAL MANAGEMENT

Surgical resection of gastric GIST

Surgical R0 resection is the standard treatment for symptomatic gastric GIST and for those larger than 2 cm in diameter. An option in primary inoperable cases is neoadjuvant imatinib therapy with the aim of achieving secondary operability[20,24,25].

Drug therapy of gastric GIST

Drug therapy with a tyrosine kinase inhibitor is indicated in patients with distant metastases[20,25]. Patients with local disease undergo initial R0 resection followed by risk stratification based on tumor location, size, and mitotic activity[22]. A 3-year course of imatinib therapy is the current standard in patients with an intermediate or high risk of tumor relapse and the appropriate mutation analysis[26]. In a controlled phase-3 study, imatinib significantly prolonged survival in GIST with a high risk of progression[26]. Both the ESMO and NCCN guidelines recommend this type of therapy for GIST patients with a significant risk of relapse[20,25]. While evidencebased recommendations are available for the treatment of clinically manifest GIST, there are no uniform guidelines for clinical management of early gastric GIST. Rossi *et al*[5] recently reported that patients with early gastric GIST have an excellent prognosis irrespective of the mitotic rate. Epidemiological data also demonstrate the generally benign behavior of early GIST of the stomach. Rossi et al. coined the term "self-limiting tumorigenesis" to describe the tumor biology of early GIST of the stomach.

Surgical resection of early gastric GIST most likely is overtreatment in older people. The well-documented, generally benign behavior and the high prevalence of early gastric GIST in the elderly argue for a conservative management. Particularly in older patients, it is important to consider not only the hospital morbidity but also the low but not negligible perioperative mortality, which may amount to 1% or higher according to the published literature[27,28]. There are no clinical studies that have demonstrated any advantage (in quality-of-life or in survival) of surgery over endoscopic surveillance in patients with early (< 1 cm) gastric GIST[6].

ENDOSCOPIC SURVEILLANCE

Endoscopic surveillance should be performed in patients with early asymptomatic GIST of the stomach. Repeat endoscopic ultrasound at 12-mo intervals is generally recommended. If the size remains constant, the intervals can probably be extended in the elderly. Interestingly to note, rapid progression of a gastric GIST that had stayed stable at a size of 1.8 cm for 8 years has been reported[29].

If initial cytohistological assessment of early gastric GIST has not been performed or has not been conclusive and if there is strong clinical suspicion of early GIST, endoscopic ultrasound of the stomach should be repeated already after an interval of 2-3 mo. This short interval is not due to the (very low) probability of rapidly progressive GIST[30] but takes into account the (low) risk of a subepithelial lesion different from GIST. The correct evaluation of a subepithelial lesion by endoscopic ultrasound relies on an experienced team of endoscopists. Indeed the differential diagnosis of "subepithelial or submucosal lesions" of the stomach is complex and extensive[10,14]. The differential diagnosis has to include cysts, pseudocysts, varices, ectopic pancreatic tissue, leiomyomas, schwannomas, lipomas, lymphomas, gastric polyps, inflammatory fibroid polyps, submucosal metastases, protruding aneurysms, large lymph nodes, granular cell tumors and gastric carcinoids[31]. Even localized protrusion of the gallbladder, spleen or left liver lobe can appear as a submucosal lesion in conventional gastroscopy.

If the first repeat endoscopic ultrasound (2-3 mo after initial diagnosis) reveals no change in size of a small (< 1 cm) subepithelial or submucosal lesion, the surveillance interval can be extended to 12 mo. However, a lesion that becomes markedly larger after 2-3 mo requires a definitive (histological) diagnosis and therapy (such as surgical resection). In addition, a gastric GIST that increases in size during follow-up has to be considered for surgery[32] and be discussed on the tumor board.

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REVIEW

Endoscopic ultrasonography for surveillance of individuals at high risk for pancreatic cancer

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Abstract

Pancreatic cancer is a highly lethal disease with a genetic susceptibility and familial aggregation found in 3%-16% of patients. Early diagnosis remains the only hope for curative treatment and improvement of prognosis. This can be reached by the implementation of an intensive screening program, actually recommended for individuals at high-risk for pancreatic cancer development. The aim of this strategy is to identify pre-malignant precursors or asymptomatic pancreatic cancer lesions, curable by surgery. Endoscopic ultrasound (EUS) with or without fine needle aspiration (FNA) seems to be the most promising technique for early detection of pancreatic cancer. It has been described as a highly sensitive and accurate tool, especially for small and cystic lesions. Pancreatic intraepithelial neoplasia, a precursor lesion which is highly represented in high-risk individuals, seems to have characteristics chronic pancreatitis-like changes well detected by EUS. Many screening protocols have demonstrated high diagnostic yields for pancreatic pre-malignant lesions, allowing prophylactic pancreatectomies. However, it shows a high interobserver variety even among experienced endosonographers and a low sensitivity in case of chronic pancreatitis. Some new techniques such as contrast-enhanced harmonic EUS, computer-aided diagnostic techniques, confocal laser endomicroscopy miniprobe and the detection of DNA abnormalities or protein markers by FNA, promise improvement of the diagnostic yield of EUS. As the resolution of imaging improves and as our knowledge of precursor lesions grows, we believe that EUS could become the most suitable method to detect curable pancreatic neoplasms in correctly identified asymptomatic at-risk patients.

Key words: Endoscopic ultrasonography; Pancreatic cancer; Surveillance

Core tip: In the era of early diagnosis and screening programs, endoscopic ultrasound (EUS) represents the most promising tool able to identify pancreatic precursor neoplasms in high risk individuals. If compared to other imaging techniques, it is highly accurate to diagnose small pancreatic cancer and pre-malignant lesions, with very low rate of complications and limitations. Here are reported the current role of EUS in various international screening programs and its future possible developments.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related death in the western world[1,2], with a median age at diagnosis of 71 years and 45220 new cases and 38460 deaths in 2013 in the United

States[3]. In contrast to other causes of cancer death (lung, colorectal, breast and prostate), which have declined in the last years, the death rate from PDAC has increased during the same time period[4]. It is a highly aggressive tumor characterized by an incidence rate almost equaling the mortality rate and an overall 5-year survival of approximately 5%-6%[1,2]. This dismal prognosis is mainly due to the fact that the tumor is characterized by a locally advanced or metastic stage at the presentation, low resection rates and poor response to radiotherapy and chemotherapy.

Even though complete resection improves median survival, at the time of diagnosis only 10% to 25% of pancreatic cancer patients will be amenable to potentially curative resection[5]. Also in this case 5-year survival remains low (10% to 24%)[6,7].

However, longer survival has been reported for complete resection of early stage tumors thus identifying patients who have early, small, localized tumors at presentation could improve this poor overall survival rate[8].

Resection of small tumors (< 2 cm or T1) improves 5-years survival (30% to 60%)[9,10]. However it has been alluded that the better prognosis is for tumors < 1 cm (T1a) with 5-years survival up to 78%[6,11,12].

To date, however, it might be difficult to detect such a small pancreas cancer, mainly due the fact that more than 90% of PDAC measuring 1 cm or less in diameter are asymptomatic.

Probably the only way to improve survival lies in identifying early disease or precursor lesions through a screening program of asymptomatic individuals.

As premalignant stages of disease have been identified, and the sensitivity of pancreatic imaging has improved with endoscopic ultrasound (EUS) and high-resolution magnetic resonance imaging (MRI), early detection of small curable pancreatic cancers and premalignant lesions now seems possible[13-16].

Unfortunately, due to the overall low incidence of the disease, accounting for 3% of all new cancer cases in the United States and a life-time risk of 1.3% in the general population, and the lack of simple, safe, accurate, inexpensive, and non-invasive diagnostic tests for early lesions, a widespread screening program does not seem feasible at present.

Multiple risk factors for pancreatic cancer development have been identified like male gender, obesity, African-American or Ashkenazi Jewish descent, nickel exposure, smoking, lack of physical activity, and calorie intake[17-20].

Beside them, also members of a family with a strong history of disease or individuals with inherited pancreatic cancer syndromes, carrying a known genetic mutation, should be considered at high risk of developing pancreatic cancer (high risk individuals, HRIs)[21-25]. Screening of these high-risk groups seems to be of benefit since genetic susceptibility and familial aggregation are responsible of 3%-16% of pancreatic cancers[26-28].

These individuals can be divided into two groups: those who belong to families in which pancreatic cancer affects at least two first-degree relatives without a known genetic mutation (familial pancreatic cancer, FPC) and those with hereditary syndromes or diseases that predispose to the development of pancreatic cancer (Table 1).

FAMILIAL PANCREATIC CANCER

The former represents the largest proportion of hereditary PDAC.

Prospective studies demonstrated an increased risk of pancreatic cancer in healthy first degree relatives (FDRs), related to the number of family members affected. This risk has been estimated to be 2.3 to 4.5-fold greater in individuals with one FDR with pancreatic cancer, 6.4-fold greater in individuals with two FDRs with the disease and 32 to 57-fold greater in individuals with three or more FDRs affected[29-32].

Similarly to other familial tumors, the median age of presentation in patients with FPC is up to 20 years earlier than in patients with sporadic cancer (49 years *vs* 61 years)[33-35] with an "anticipation phenomenon" in the affected kindred and a trend to become more severe and appear at an earlier age as the disorder is passed from one generation to the next[35,36]. Currently, the genetic etiology of most cases of FPC remains undetermined but complex segregation analysis of these patients has led to the discovery of various candidate pancreatic cancer susceptibility genes such as BRCA2 (6%-17% of cases)[37,38], partner and localizer of BRCA2 (PALB2) (1%-4% of cases)[39,40] and palladin, even if mutations of the latter have been identified in normal controls as well[41-43].

Due to the complex nature of pedigrees, a Mendelian risk prediction tool for PDAC, named PancPRO was developed in 2007.

This is a prediction model for FPC that, using full pedigree data and age of family members, estimates the probability that an asymptomatic individual will develop the disease[44].

INHERITED PANCREATIC CANCER SYNDROMES

Individuals with certain tumor syndromes have a marked increase in risk of developing pancreatic ductal adenocarcinoma.

These syndromes are represented by familial atypical mole-multiple melanoma, Peutz-Jeghers syndrome, hereditary pancreatitis, cystic fibrosis, familial breast-ovarian cancer, hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, Li-Fraumeni syndrome.

Familial atypical mole-multiple melanoma

Familial atypical mole-multiple melanoma (FAMMM) is an autosomal dominant disease associated with mutations within CDKN2A gene (p16 Leiden)[45,46]. Its inactivation is associated with PDAC that was found 13 to 38-fold more frequent than expected[46,47], with a cumulative risk

Table 1 Genetic diseases associated with pancreatic cancer risk

Risk condition	Relative risk	Risk by age 70	Gene
Familial pancreatic cancer			*PALLD*
1 first-degree relative	2.3-4.5	2%	*BRCA2*
2 first-degree relatives	6.4-18	3%	*PALB2*
⩾ 3 first-degree relatives	32-57	16%	
Familial atypical multiple mole melanoma	13-38	15%-20%	*CDKN2A/p16*
Peutz-Jeghers Syndrome	132	11%-60%	*STK11/LKB1*
Hereditary pancreatitis	50-87	30%-75%	*PRSS1*
			PRSS2
			SPINK1
			CTRC
Cystic fibrosis	5.3	<5%	*CFTR*
Familial breast ovarian cancer	3.5-10	5%	*BRCA2*
	2.3-3.6	1%	*BRCA1*
Hereditary non-polyposis colon cancer	2.3-8.6	3%-4%	*MLH1*
			MSH2
			MSH6
Familial adenomatous polyposis	4.5-5	2%	*FAP*
			MUTYH
Li Fraumeni sindrome	Unknown	Unknown	*TP53*

by age 75 of 15% to 20%[48,49].

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal dominant genetic disease characterized by an increased risk of various neoplasms, including pancreatic cancer[50,51] and it is often associated with mutations within *STK11* gene, a tumor suppressor gene. Patients with PJS have a 132-fold increased risk[50] and an 11%-36% cumulative risk of developing PDAC with an early age of onset (average: 40.8 years)[50,52]. In this kind of patients, it frequently develops through IPMN[23,53].

Hereditary pancreatitis

Hereditary pancreatitis (HP) is an inherited form of chronic pancreatitis characterized by mutations within *PRSS1*, *PRSS2*, *SPINK1*, *CFTR* and *CTRC* genes[54,55]. PDAC is often a consequence of this condition[56,57] insomuch so resected pancreata from patients with HP frequently demonstrated PanIN-3 lesions (50%)[58]. Patients with hereditary pancreatitis have a 53 to 87-fold increase risk[57,59] with an age of onset at 50 years in smokers[60]. Lifetime risk is 30% to 75% in patients with paternal inheritance[57,59].

Cystic fibrosis

Cystic fibrosis (CF) is a disorder associated with mutations within CFTR gene with an increased risk for PDAC (5.3-fold)[61], in fact the histological aspect of CF associated lesions is very similar to that of "classical" chronic pancreatitis, characterized by atrophy of acinar tissue, fibrosis, and inflammation[62,63].

Familial breast-ovarian cancer

Familial breast-ovarian cancer (FBOC) is an autosomal dominant inherited disease due to mutations within *BRCA1* or *BRCA2* genes.

The risk of PDAC among BRCA1 mutation carriers is low (2.3-3.6 fold than general population)[64,65]. Conversely BRCA2 mutation carriers had a 3.5-10-fold increased risk[66,67] and a 5% lifetime risk of pancreatic cancer[67].

Hereditary non-polyposis colorectal cancer

Hereditary non-polyposis colorectal cancer (HNPCC) is an autosomal dominant genetic condition due to the inherited mutations in DNA-mismatch repair genes, such as *MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM*[68]. The estimated relative risk of pancreatic cancer is 2.3 to 8.6-fold higher with a lifetime risk of pancreatic cancer (3%-4%)[69,70]. Carriers of MLH1 mutations have a higher risk than carriers of MSH2 (5.6 *vs* 2.3)[71].

Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant disease of the colon caused by mutations within the gene *APC*. Among FAP pediatric carriers, pancreatoblastoma may represent an extracolonic manifestation of FAP[72]. The relative risk for pancreatic cancer is 4.5 in patients with the syndrome[73] and the lifetime risk 2%[74].

Li-Fraumeni syndrome

PDAC seems to be a part of the cancer spectrum of the Li-Fraumeni syndrome (LFS), a disease caused by mutations within *TP53* gene[63,75]. It is has been estimated that about 1.3% of these patients show pancreatic cancer[63,76].

PRECURSOR LESIONS

The ideal screening method for HRIs should detect small asymptomatic pancreatic cancers and, mainly, benign non-invasive precursor lesions, to allows for curative surgical resection[77,78]. In fact pancreatic carcinogenesis should be intended as a multistep phenomenon with progressive changes from the normal pancreatic ductal epithelium to infiltrating carcinoma[79].

The other three well known precursor lesions are: pancreatic intraepithelial neoplasms (PanINs), intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs)[78-81].

Pancreatic intraepithelial neoplasia

PanINs are usually asymptomatic and are characterized by microscopic papillary or flat, noninvasive epithelial neoplasms that are usually < 5 mm in diameter and confined to the pancreatic ducts[78,82].

According to the degree of cytological and architectural atypia, PanINs are divided into three grades[83]: PanIN-1: minimal atypia; flat (PanIN-1A) and papillary types (PanIN-1B); PanIN-2: moderate atypia; PanIN-3: severe atypia.

The evidence that this kind of lesions are linked to invasive carcinoma is based on clinical associations and

genetic analysis[81,84-86].

Mucinous cystic neoplasms

Mucinous cystic neoplasms (MCNs) are cystic epithelial neoplasms that occur almost in women, lack of communication with the pancreatic ductal system and have a predilection for the body and tail[80,87].

Malignancy rates of resected MCNs vary from 6% to 36%[80] and usually resembles common ductal adenocarcinoma.

Intraductal papillary mucinous neoplasms

Intraductal papillary mucinous neoplasms (IPMNs) are a more aggressive neoplasm compared to MCNs. They represent a disorder of the pancreatic ductal system, characterized by cystic dilatation. Clinically, three different varieties exist: main duct type characterized by diffuse dilatation of the main pancreatic duct, branch duct type (IPMN-BD) appearing as dilatation of branch ducts, and mixed-type involving both of them.

These lesions are thought to undergo transformation from adenoma to borderline neoplasms, and finally to carcinoma, similarly as seen with PanINs.

Patients with IPMN-MD have a risk of malignancy of approximately 50%-90%[16,86-89], *vs* 6%-46% in patients with IPMN-BD[16,87,89,90]. In these patients, the risk of malignancy increases with presence of symptoms, mural nodules and size over 3 cm[89]. IPMNs are mainly present in familial pancreatic cancer kindred and in PJS and FAP patients where seems to have a more aggressive biological behavior (increased growth rate and degeneration) compared to sporadic IPMNs[22,91]. IPMNs are more prevalent in high risk individuals than in the general population (16%-42% *vs* 0.2%)[92], moreover they are commonest in specimens from FPC than in sporadic PDAC (33% *vs* 6%)[81].

SCREENING

The goal of screening could be the reduction of pancreatic cancer-related mortality. As previously reported, surrogate end point in pancreatic cancer could be the identification and resection of potentially curable lesions (high-grade precursors and early invasive carcinomas). There is no evidence that diagnosing these lesions will improve survival, but there are data suggesting that resection of very early disease is associated with better prognosis[93,94]. However, no consensus opinion could be reached on the best suitable approach for screening until available imaging modalities and biomarkers will become adequate to detect early stage cancer. Actually, serum markers, computed tomography, magnetic resonance (MRI) ± cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography and endoscopic ultrasound haven't all the features of an effective screening tool[95-100]. Describing the screening modalities is beyond the aim of this review. Whatever the approach a surveillance program should be recommended for patients with a risk of PDAC development greater than 10-fold[22,23,77].

This degree of risk includes family members with ⩾ 3 first-degree relatives with pancreatic cancer and patients with hereditary pancreatitis, FAMMM and PJS.

A screening test should also be performed in individuals with syndromes associated with pancreatic cancer and known high-risk factors, such as cystic neoplasia, duct ectasia, diabetes mellitus, smoking history and chronic pancreatitis[101]. To evaluate the risk to develop pancreatic cancer can be used mathematical models, such as the PancPRO model (see above).

No clear consensus was achieved on when to start screening. It seems reasonable to start at 40-50 years of age (30 years for PJS) or 10-15 years earlier than the younger kindred affected by pancreatic cancer[21,22,96,102].

There is no consensus also on the frequency, because evidence on the natural history and rate of progression of pancreatic cancer in high risk patients is still lacking. However, yearly screening seems to be the most suitable approach[21,22,36,103] even if some centers recommend 3 years intervals in case of negative screening exam and absence of other risk factors associated. A more aggressive protocol can be used for patients with abnormal findings at the last screening[52]. In these cases a subsequent screening could be done every 3-6 mo[22,103] or every 3-12 mo[21,36,100].

The majority of studies have generally used the same imaging test for surveillance as for baseline screening, while others suggest an alternating use of MRI/MRCP and EUS[36,98](Figure 1).

ROLE OF ENDOSCOPIC ULTRASONOGRAPHY

Endoscopic ultrasonography (EUS) is known as a powerful imaging tool for studying pancreatic diseases. In particular it has been described as a very accurate imaging technique for early detection of pancreatic cancer providing high-resolution images of the pancreas without the risk of radiation exposure and identifying mural nodules (focal thickening of the wall in branch duct IPMNs), which are associated with increased risk of malignancy[16,82]. With its high resolution, in experienced hands it is able to detect focal lesions as small as 2-5 mm[22,104-106] with the possibility of taking bioptic samples by fine needle aspiration (FNA) for histopathological examination. EUS has been described as a highly sensitive method for pancreatic malignancy[107], but results for accuracy differ. Early studies have shown a better accuracy in detecting PDAC for EUS compared with dual phase helical CT (97% *vs* 73%, respectively)[108]. This results were also confirmed when EUS was compared with multiphase helical CT (98% *vs* 86%, respectively[107,109]. The prospective CAPS3 study is the first blinded study that compared standardized pancreatic protocol CT, secretin-enhanced MRI/MRCP and EUS for one-time screening in HRIs. It showed that EUS and MRI are better than CT for the detection of small, cystic, pancreatic tumors, with a diag-

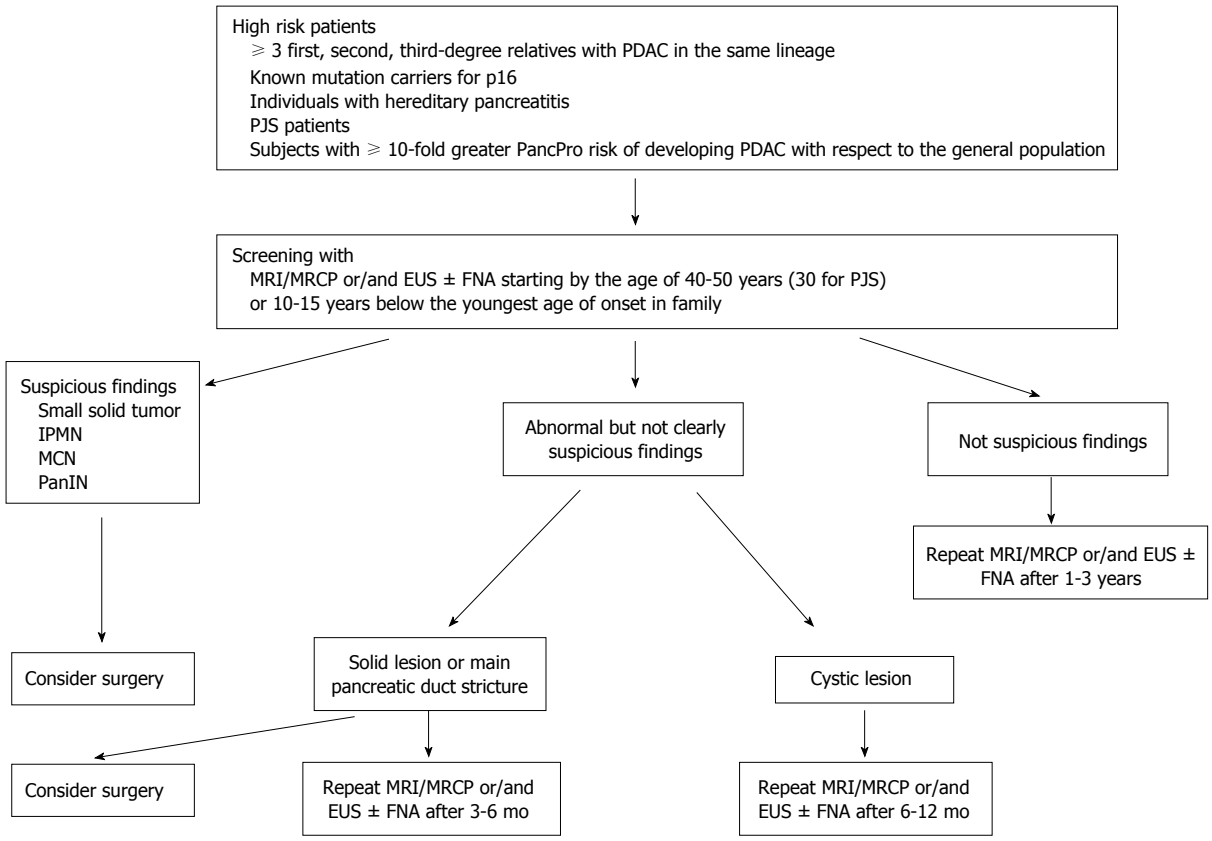

Figure 1 Management algorithm for individuals at risk of pancreatic cancer. EUS: Endoscopic ultrasonography; ERCP: Endoscopic retrograde cholangiopancreatography; CT: Computed tomography; FNA: Fine needle aspiration; PDAC: Pancreatic ductal adenocarcinoma; PJS: Peutz-Jeghers syndrome; MRI: magnetic resonance imaging; MRCP: Magnetic resonance cholangiopancreatography; IPMN: Intraductal pancreatic mucinous neoplasia; MCN: Mucinous cystic neoplasm; PanIN: Pancreatic intraepithelial neoplasia.

nostic yield of 42.6%, 33.3% and 11%, respectively[110]. EUS was also found to be superior to MRI and CT in sensitivity regarding the detection of IPMN-derived and -concomitant PDACs at the first examination (100% *vs* 53% and 53% and 61% *vs* 33% and 39%, respectively) and during a 5 years follow-up period (100% *vs* 50% and 56%, respectively)[111]. In this setting EUS detected PDCAs significantly better than the other modalities and it appears to be more useful than CT and MRI for the early detection of pancreatic cancer (Table 2).

Another recent study[112] has shown an incremental increase in diagnostic yield of EUS-FNA over CT (36%) and MRI (54%) for prediction of a neoplastic cyst and an increase in overall accuracy for diagnosis of neoplastic pancreatic cysts by the addition of EUS±FNA.

A normal EUS examination seems to have a high negative predictive value (NPV)[113]. Two recent studies including patients with suspicion of pancreatic cancer followed for 23.9 and 25 mo, respectively, showed that none of those with a normal EUS evaluation developed pancreatic cancer (NPV = 100%)[114,115].

Furthermore, EUS-guided fine needle aspiration (EUS-FNA) may provide a histological diagnosis of cancer and a means of detecting dysplasia in precancerous lesions[23]. A recent meta-analysis has demonstrated that EUS-FNA is highly sensitive (89%), specific (96%), accurate (97%) and has a very good positive likelihood ratio (16.08) and an acceptable negative likelihood ratio (0.13)[116]. Moreover, another recent study not included in the meta-analysis previously reported[117], confirmed these values and has shown that the diagnostic accuracy of EUS-FNA could be further improved by the addition of pancreatic juice analysis.

EUS complications are rare and the risk of perforation is similar to standard upper endoscopy (< 0.03%). Also EUS-FNA of pancreatic lesions can be considered a safe technique, especially if several technical points are taken into account in each specific situation the endosonographer perform a FNA[118]. The two major complications after a FNA are pancreatitis (0%-2%)[119,120] and bleeding (0% to 1.3%)[121,122], while the risk of infection exists only when mucinous cystic lesions are involved[118]. No deaths were reported[120-123].

Actually, the diagnosis of PanINs by imaging tests is very challenging. The surgical resection of early curable neoplasms detected during screening programs in at-risk individuals has permitted to study the morphology of unadulterated precursor lesions in this kind of patients[21,81]. In particular: (1) PanINs are frequently associated with lobulocentric atrophy and fibrosis; and (2) PanINs are often multifocal.

The combination of these alterations produces grossly appreciable changes in the pancreas with a mosaic of fibrosis, atrophy and uninvolved parenchyma, very similar

Table 2 Endoscopic ultrasound-based studies on screening for individuals at risk for pancreatic cancer

Ref.	No. of patients	High-risk groups	Imaging test	Target lesions	Diagnostic yield	Limits of the study
Brentnall *et al*[21]	14	FPC	EUS + ERCP + CT	PanIN ⩾ 2	50%	
Kimmey *et al*[104]	46	FPC	EUS	PanIN ⩾ 2	26%	
Canto *et al*[22]	38	FPC, PJS	EUS	IPMN, PC	5.30%	Low PPV
Canto *et al*[23]	78	FPC, PJS	EUS	IPMN, PC, PanIN ⩾ 2	10.20%	
Poley *et al*[135]	44	FPC, PJS, FAMMM	EUS	IPMN, PC	22.70%	No pathological confirmation of IPMN
Langer *et al*[103]	76	FPC, FAMMM	EUS + MRCP	IPMN	1.30%	Moderate risk patients
Verna *et al*[162]	51	FPC, FBOC	EUS and/or MRCP	IPMN, PC, PanIN ⩾ 2	12%	
Schneider *et al*[36]	72	FPC, FAMMM	EUS + MRCP	IPMN	12.50%	No pathological confirmation
Canto *et al*[110]	216	FPC, FBOC, PJS	EUS + CT + MRCP	IPMN, PC	39%	Mainly no pathological confirmation

FPC: Familial pancreatic cancer; PJS: Peutz-Jeghers syndrome; FAMMM: Familial atypical multiple mole melanoma; FBOC: Familial breast ovarian cancer; EUS: Endoscopic ultrasonography; ERCP: Endoscopic retrograde cholangiopancreatography; CT: Computed tomography; MRCP: Magnetic resonance chol angiopancreatography; PanIN: Pancreatic intraepithelial neoplasia; IPMN: Intraductal pancreatic mucinous neoplasia; PC: Pancreatic cancer; PPV: Positive predictive value.

to chronic pancreatitis[81,124].

These quite subtle ductal and parenchymal changes are often detectable by EUS using standard criteria for the diagnosis of chronic pancreatitis, such as heterogeneity, multifocal lobularity, echogenic foci, hypoechoic nodules, strands and dilated main and branch pancreatic ducts[22,124,125].

In literature, chronic pancreatitis-like changes are found in variable rates. The John Hopkins group detected these findings in 45% and 61% of the examined HRIs in whom they were significantly more common, compared with control subjects, regardless of age and alcohol exposure[22,23]. This ultrasonographic diagnosis of chronic pancreatitis was surgically confirmed in all but one of the HRIs who underwent surgery. Furthermore, all but 1 of these patients had branch duct-type IPMNs[22]. In the University of Washington study, the authors suggested that the pancreatitis-like changes, which are part of the phenotype of FPC kindreds, are expression of un underlying pancreatic dysplasia rather than chronic pancreatitis[21]. Finally the German group reported a relative low prevalence (22.4%) with all but one normal findings at MRI/MRCP evaluation[103].

These studies suggest that features of chronic pancreatitis should be noted during screening because although the precursor lesions may be too small to visualize by currently available imaging technologies, the effects they produce such as cysts and nodules in a background of intact parenchyma, can be detected by EUS in the hands of an experienced operator.

This was also confirmed in IPMNs. In a recent study conducted on forty patients, who underwent resection for IPMN, PanIN was researched on surgical specimens and the pathological data were compared with endosonography features. EUS changes corresponded to PanIN lesions in 83% of cases and it was able to detect 69% of patients with PanIN lesions (57% of those with panIN-3)[126].

Nevertheless, the presence of a chronic pancreatitis drastically reduces the diagnostic value of EUS, because of the intraductal and parenchymal changes associated with chronic inflammation and fibrosis could not to be differentiated from premalignant pancreatic lesions[127].

In summary the clinical significance of these changes in HRIs remains unclear. They may be indicative of a precursor lesion of PDAC, but these data must be carefully assessed.

Another field of application for EUS in HRIs is in differentiation between focal pancreatitis and pancreatic cancer. Contrast enhanced EUS seems to be a promising technique due to perfusion characteristics of microvessels[128]. Hocke *et al*[129] analyzed the sensitivity and specificity for the diagnosis of pancreatic carcinoma of conventional endoscopic B-mode, power Doppler ultrasound and contrast-enhanced power mode. They reported an increase from 73.2% to 91.1% and from 83.3% to 93.3% respectively, with the use of contrast-enhanced power mode *vs* conventional EUS. The major limits of EUS are: (1) high interobserver variety, even among experienced endosonographers, especially for diagnosis of pancreatitis like changes[130,131]; (2) the need for sedation because of the minimally invasive nature of the procedure; (3) the need of additional clinical and imaging information[112] to improve accuracy as demonstrated by Meining *et al*[132] who reported a worse overall accuracy for a strictly blinded EUS examinations (61.1%) compared to the accuracy of routine and unblinded evaluation with additional imaging information (72.2% and 75.0%, respectively); (4) Low sensitivity in case of chronic pancreatitis, diffusely infiltrating cancer and a recent episode of acute pancreatitis[133,134]; and (5) Low availability outside major centres.

Currently, many international screening protocols are available throughout the world and the majority of them use EUS as the main imaging tool for screening, because of its ability to detect masses < 1 cm[21-23,132,135], with CT or MRI/MRCP scans and ERCP proposed in combination with EUS[136].

The first EUS-based screening program was prospectively conducted by Brentnall *et al*[21] at the Washington University, on a small group of 14 high-risk patients from three unrelated pancreatic cancer kindred that had two

or more affected members in at least two generations. The study evaluates an EUS- and ERCP-based approach with the aim to detect pancreatic cancer precursor lesions (PanINs). The EUS and ERCP suspected signs of PanINs were no specific chronic pancreatitis-like changes. Seven patients (50%) had an abnormal EUS and ERCP histological confirmed as precancerous changes in the pancreas (PanIN-2 and 3) without any invasive cancer.

A follow up study of the same group confirmed a high yield (26%). It was based on a large cohort of 46 patients and was conducted using EUS as the first diagnostic approach, with ERCP for patients with EUS abnormalities. Twelve patients with imaging abnormalities were referred to histological examination and all of them revealed widespread precancerous lesions (PanIN 2 e 3), without evidence of invasive pancreatic cancer[136].

Canto *et al*[23] screened HRIs for early pancreatic neoplasia with an EUS-based and an EUS- and CT-based[22] prospective controlled study at Johns Hopkins University. In the former approach they used EUS to screen 38 asymptomatic individuals from high risk families (≥ 3 affected relatives and PJS). Six pancreatic lesions were detected: four benign masses and two neoplastic (one adenocarcinoma and one IPMN; screening yield of 5.3%). Either the CT or ERCP evaluations did not detect the single PDAC. In the latter one, pancreatic abnormalities were compared in 78 high-risk individuals (72 from FPC kindred and 6 PJS) and 149 control patients. If the EUS was abnormal, EUS-FNA and ERCP were performed. This approach found 8 patients with pancreatic neoplasms (10.2%) confirmed by surgery or FNA (6 patients had benign IPMNs, 1 had an IPMN with invasive ductal adenocarcinoma and 1 patient had PanIN-3) and no pancreatic neoplasia among the control subjects. All of the lesions visualized by CT were also detected by EUS, while CT missed two IPMNs > 1 cm in the second study and one pancreatic cancer in the first one. Moreover, ERCP correctly diagnosed only 2 of the 7 confirmed IPMNs seen by EUS.

In contrast to these findings, Langer *et al*[103] published their results of a prospective screening study conducted by the National German Familial Pancreatic Cancer Registry (FaPaCa) on 76 individuals from 34 FPC and FAMM kindreds. The protocol included CA 19-9 and CEA serum values, EUS, and MRI combined with MRCP at the screening visit. EUS-FNA was performed in the case of indefinite abnormalities and in case of diffuse parenchymal irregularities. Only three serous cystoadenoma, one IPMN, three PanIN 1 and one PanIN 2 were pathologically confirmed. Three of them, the smaller ones, were detected by EUS, but not by MRI. No cancers were identified and only IPMN was considered a significant precancerous lesion for a diagnostic yield of 1.3%.

This lower yield could be explained by the fact that this study included also a large number of patients at a moderate risk (< 10-fold) with a fraction of high-risk patients of 42% *vs* 55% for the second study of the Johns Hopkins University. Moreover, PanIN 1 e 2 and serous cystoadenoma were not considered precancerous lesions. During long term follow-up[36] (24 mo-extended surveillance), this study showed histologically proven precancerous or cancerous lesions in 4 individuals (5.5%) and additional branch duct IPMN in 5 ones, with a diagnostic yield of up to 12.5%, close to the previous rates reported by the Johns Hopkins and the Rotterdam groups.

In comparison, Poley *et al*[135], of the Dutch group, published the results of a prospective study using EUS in 44 asymptomatic high risk family members with FPC, BRCA1, BRCA2, or p16 germline mutation carriers, and patients with PJS. They found asymptomatic PDAC in three patients (6.8%, two with lymph node metastases), and seven IPMNs (16%). Their high yield (22.7%) may be related to the selection of known carriers of mutations at high risk to develop pancreatic cancer with a higher fraction of individuals at elevated risk.

Nevertheless, it has to be pointed out that IPMNs in both German study and in the Dutch study are EUS-diagnosis, not histologically confirmed. The 12.5% and 16% results may as well represent overestimations.

COST EFFECTIVENESS

A screening test can be considered successful if the benefits/costs ratio is favourable. As previously reported, a EUS-based screening allows an early diagnosis of PDAC, while it is not still clear if this approach could be considered cost-effectiveness.

Rulyak *et al*[137] compared one-time EUS-based screening to no screening in a hypothetical cohort of 100 members 50 years old of FPC kindred. The life time medical costs and life expectancy were compared, assuming a 20% prevalence of pancreatic dysplasia and 90% sensitivity of EUS and ERCP. They demonstrated that endoscopic screening of these individuals increases patient life expectancy (38 years, similar to other common preventive medical interventions) in a cost-effective manner ($16885 per life-year saved on the base-case ICER, an indicator which take into account the third-part payer and the societal perspectives). Only patients with a pre-test probability of pancreatic dysplasia of 16% or greater and individuals under 70 years of age seem to have benefits from this approach. Moreover, the sensitivity of EUS and ERCP must be at least 85% in order for screening to be effective. The cost-effectiveness of repeated screening was not determined.

In contrast, Rubenstein *et al*[138] have performed a clinical and economic evaluation of EUS for 45 years-old male first degree relatives with chronic pancreatitis diagnosed by EUS on screening exam. They compared 4 strategies: do nothing, prophylactic total pancreatectomy, EUS and EUS-FNA and assessed mortality, quality of life, complications and costs. They addressed the inferiority of EUS compared to a no-screening approach because of the low sensitivity of EUS in the presence of chronic pancreatitis-like changes. EUS-FNA provided intermediate results. The prophylactic total pancreatectomy could be considered the better approach in terms od life expectancy if the lifetime risk of pancreatic cancer is

46% or greater.

These studies are based on one-time screening and so are not applicable to a individuals who require repeated screening examinations during their life. A review conducted by Latchford *et al*[139] focused on a cost-effectiveness analysis of a screening program in PJS, based on EUS and ERCP for molecular analysis of pancreatic juice. According to this review, patients with suspicious findings would be offered CT, all others should repeat screening 1-3 years later, based on risk stratification detrmined by molecular tests. With this approach over a 35-year period of annual EUS, 3780 screens would be carried out and only those with morphological changes found on EUS are offered CT and ERCP.

This model can give an estimate of costs of about $372708 per life saved. This cost could be further reduced to $297000 per life saved by molecular analysis of pancreatic juice. In this case, in fact, most individuals would only be screened every 3 years thanks to more accurate risk stratification.

FUTURE PERSPECTIVES

In the near future, the development of EUS technology should help us to screen HRIs.

Contrast-enhanced harmonic endoscopic ultrasonography (CH-EUS) visualizes parenchymal perfusion in the pancreas without Doppler-related artifacts[140,141]. It could play a central role associated to EUS-FNA when the latter gives a negative finding in a suspected lesion. Two recent studies[141,142] showed a higher sensitivity of CH-EUS compared to EUS-FNA for the identification of pancreatic carcinoma. Most of false-negative EUS-FNAs resulted to have a hypoenhancement on CH-EUS examination. Moreover, Kitano *et al*[142] found that CH-EUS when combined with EUS-FNA is able to increase the sensitivity from 92.2% to 100% and is superior to MDCT in diagnosing small (< 2 cm) carcinomas, identifying 9 tumours missed by MDCT. Fusaroli *et al*[143] also reported that CH-EUS allowed the detection of small lesions in patients with uncertain EUS findings because of chronic pancreatitis. In addition, CH-EUS allows to focus on the lesion target for EUS-FNA.

Diagnostic accuracy of EUS-FNA will be also enhanced by the detection of DNA abnormalities as k-ras point mutations and microsatellite losses[144,145] or novel protein markers such as mesothelin[146,147] and prostate stem cell antigen[147]. Their detection in EUS-FNA specimens may provide confirmation of the presence or absence of malignancy and should negate the need for further testing.

Characterization of pancreatic cysts has become essential for definitive surgical treatment or ongoing surveillance. However, current diagnostic methods (cross-sectional imaging, EUS, and fluid analysis including cytology, fluid characteristics, chemistry, and tumor markers) do not allow an accurate differentiation between the various types of cysts[148,149]. A novel needle-based confocal laser endomicroscopy (nCLE) miniprobe that can be passed through a 19-G EUS-FNA needle enables real-time imaging with microscopic detail. A pilot study[150] suggests that nCLE can detect mucinous pancreatic neoplasms with excellent specificity and PPV (100% for both of them) but a low sensitivity and NPV (59% and 50%, respectively) with an overall complication rate of 9%.

Finally, computer-aided diagnostic techniques, yet used in some screening programs[151,152], could be added to standard EUS images for the differentiation of pancreatic carcinoma from chronic pancreatitis[151,153]. With digital image processing and computer-aided EUS image differentiation technologies, physicians could use the computer output as a "second opinion" and make the final decisions as reported by the high diagnostic accuracy (98%) of a recent study[154].

CONCLUSION

These data demonstrate that screening with EUS, preferably associated with MRCP, as reported by International Cancer of the Pancreas Screening summit (83.7% agree for EUS and 73.5% agree for MRI/MRCP)[96] is feasible and can detect curable pancreatic neoplasms in correctly identified asymptomatic at-risk patients. In particular, as reported by Ludwig *et al*[155], EUS could be subsequent to an MRCP as initial imaging. This approach should reduce the number of false positives (patients with abnormal MRCPs who on EUS had no appreciable lesion) avoiding unnecessary surgery. The two modalities may complement each other. In fact, MRI/MRCP, in contrast with EUS, is able to image the entire abdomen and pelvis, an useful feature for patients at risk for multi-organ cancer, but has a low sensitivity in detecting PanIN lesions and small (< 1 cm) pancreatic cancer, even if recently there has been the development of 3T MRI scanners able to detects small tumors in asymptomatic patients through indirect signs (black and white sign) and cystic lesions ⩾ 3 mm[99,156]. MRCP is superior to EUS in delineating lesions involving the pancreatic ductal system[97,98] even if a recent study[157] has shown similar results between three dimensional CEUS and MRI in evaluating IPMNs smaller than 1 cm. Nevertheless EUS can image mural nodules associated with increased risk of malignancy.

It is also strongly suggested that surveillance programs should be performed by a center with experience in the specific pathology within the context of peer reviewed protocols to reduce interobserver disagreement[100].

Indeed, EUS is an operator-dependent technique that requires considerable skills and training in EUS is essential to gain experience to reliably examine the pancreas. The intensity and length of training, the requisite curriculum and the minimum number of procedures required to ensure competency are not well-defined[158].

Some experts recommend a minimum of 75 pancreatobiliary procedures and 25 cases of pancreatic FNA[159], others suggest a minimum of 30 supervised EUS-FNA

on pancreatic lesions[160] while someones believe that the majority of trainees will require double the number of proposed procedures to achieve competency in EUS[161,162].

An extensive use of CT or ERCP should be avoided in screening programs that require repeated exams in healthy individuals who have only a statistical risk of cancer.

However, a number of questions remain to be answered. What are the significance and natural history of EUS-detected chronic pancreatitis-like abnormalities? What is the clinical significance of PanIN with moderate dysplasia? Should it always be treated with pancreatectomy? How to manage the IPMN-like cystic lesions frequently found in HRIs? Should be offered surgery or a wait-and-see policy can be adopted?

As the resolution of imaging improves and as our knowledge of precursor lesions grows, we believe that these questions will be answered in the future.

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REVIEW

Advanced endoscopic submucosal dissection with traction

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Abstract

Endoscopic submucosal dissection (ESD) has been established as a standard treatment for early stage gastric cancer (EGC) in Japan and has spread worldwide. ESD has been used not only for EGC but also for early esophageal and colonic cancers. However, ESD is associated with several adverse events, such as bleeding and perforation, which requires more skill. Adequate tissue tension and clear visibility of the tissue to be dissected are important for effective and safe dissection. Many ESD methods using traction have been developed, such as clip-with-line method, percutaneous traction method, sinker-assisted method, magnetic anchor method, external forceps method, internal-traction method, double-channel-scope method, outerroute method, double-scope method, endoscopic-surgical-platform, and robot-assisted method. Each method has both advantages and disadvantages. Robotic endoscopy, enabling ESD with a traction method, will become more common due to advances in technology. In the near future, simple, noninvasive, and effective ESD using traction is expected to be developed and become established as a worldwide standard treatment for superficial gastrointestinal neoplasias.

Key words: Endoscopic submucosal dissection; Traction; Early gastric cancer; Early esophageal cancer; Early colonic cancer

Core tip: Endoscopic submucosal dissection (ESD) is associated with several adverse events, therefore, it requires more skill. Adequate tissue tension and clear visibility of the tissue to be dissected by traction are important for effective and safe ESD like surgery. Many ESD methods with traction have been reported until now. We review these ESD methods not only for early stage gastric cancer but also for early esophageal cancer or colonic cancer. We highlight both advantages and disadvantages of these methods.

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INTRODUCTION

The possibility of expanding the use for endoscopic treatment for early stage gastric cancer (EGC) has been proposed[1]. Endoscopic submucosal dissection (ESD) for EGC has improved the rate of successful *en bloc* resection[2-6] compared to endoscopic mucosal resection (EMR). ESD enables resection *en bloc* for larger lesions, those with ulceration, and those located in difficult sites. Therefore, ESD has been established as a standard treat-

ment for EGC in Japan and has spread worldwide. This method has been used not only for EGC but also for early esophageal and colonic cancers. However, ESD is associated with several complications, such as bleeding and perforation, which requires more skill. Traction is a standard method for maintaining a clear field of vision and to facilitate in the cutting of lesions during surgery. Likewise, adequate tissue tension and clear visibility of the tissue to be dissected by traction are important for effective and safe ESD[7-9].

The simplest method to achieve traction is position change[8,9]. The weight of the lesions and fluid injected to the submucosal layer enables the lesions to be hung from the wall of the gastrointestinal tract due to gravity. Endoscopic submucosal dissection becomes easier because the submucosal layer becomes wider and the field of vision becomes clearer. However, it is sometimes difficult because of limitation of position change and extension of the GI tract due to inner gas.

Recent reports on ESD with traction are described in this article (Table 1).

ESD WITH TRACTION IN UPPER GASTROINTESTINAL TRACT

Foremost, Hirao *et al*[10] reported on an EMR procedure using double endoscopes under general anesthesia, which was similar to surgery about 25 years ago. The lesion was grasped and lifted using grasping forceps through the thin endoscope, and submucosal dissection was done using a needle knife through the main scope (Figure 1). This method was revolutionary at that time; however, it was complicated and invasive. It required two endoscopic systems and more than two endoscopists and two assistants. Furthermore, two endoscopes couldnot be moved easily and independently because of their combined diameter. Thereafter, many kinds of less complicated and invasive methods have been developed.

Clip-with-line method

Lee *et al*[8] and Oyama *et al*[11] reported on the clip-with-line method, which is a simple, easy and useful method for traction not only for gastric ESD (Figure 1) but also for esophageal (Figure 2), colonic, and duodenal ESD. A long silk line is tied to the arm part of the clip, and the submucosal side of the target lesion is grasped. The line is pulled very gently. This method creates a clear field of vision. Jeon *et al*[12] and Ota *et al*[13] reported on similar methods. However, the traction direction by the clip-with-line method is limited. The pulley method is useful for pulling the line to the anal or opposite side (Figure 3). The line is captured by the second clip and fixed at the opposite side of the stomach. The first clip can be pulled to the anal side with the second clip acting like a pulley. Li *et al*[14] reported on similar method.

Percutaneous-traction method

Kondo *et al*[15] reported on percutaneous traction-assisted EMR for gastric neoplasias, which requires a laparoscopic port with a trocar (Figure 4). A small snare is introduced into the gastric lumen through a gastric port to grasp and pull the lesions away from the muscularis propria. Thereafter, von Delius *et al*[16] reported on similar methods using a PEG-minitrocar for the gastric mucosa, and Chen *et al*[17] reported on methods using a looped insertion wire for the esophageal lesions. The loop end of the wire inserted through the PEG route was grasped using biopsy forceps and pulled into the esophagus. The wire was fixed on the proximal edge of the resected mucosa with a clip. The wire was gently pulled out through the PEG route, and the edge of the resected mucosa pulled away from the muscle layer. Nishiwaki *et al*[18] reported on transgastrostomic endoscopy-assisted ESD after percutaneous endoscopic gastrostomy. A small-caliber endoscope was inserted through the mature gastrostomy, and the edge of the resecting specimen was grasped to achieve traction. However, these methods are invasive and cannot be used for lesions on the anterior wall or high fundus of the stomach. They are also sometimes difficult to control the traction direction.

Magnetic anchor method

Kobayashi *et al*[19] and Gotoda *et al*[20] reported on a magnetic anchor system. The magnetic anchor with magnetic weight and microforceps is placed at the mucosal edge. ESD is done with suitable tension by using a high-power electromagnet placed outside the body. However, this system requires large and expensive instruments.

External forceps method

Imaeda *et al*[21,22] reported on ESD using external grasping forceps. An external pair of grasping forceps is used with a second pair (Figure 5A). This method is useful for creating a clear field of vision due to not only pull but also push and gravity, for lesions in the gastric body but also for those in the antrum (Figure 5B); however, for lesions in the cardia and the lesser curvature or posterior wall of the upper gastric body, this method is sometimes difficult. This procedure does not require any assistant to hold the forceps during ESD because the handle is locked. One endoscopist can easily and independently move the endoscope and forceps. Moreover, this procedure can also enable release and regrasping of the lesion with the forceps if the traction is not sufficient. Great care must be taken to avoid damaging the mucosa, especially at the esophagocardial junction, and the overtube is necessary. Although the traction direction is limited, the forceps can always be used to raise the grasped side of the lesion.

Internal traction method

Several internal traction methods have been reported. A

Table 1 Advantages and disadvantages of the traction endoscopic submucosal dissection methods

	Traction			Other advantages	Other disadvantages
	Push	Control of direction	Control of tension		
ESD with traction in upper gastrointestinal tract					
Clip-with-line method[8,11-14]	-	-	+	Simple, easy	
Percutaneous-traction method[15-18]	+	+	+	Regrasping	Invasive
Magnetic anchor method[19,20]	+	+	+		Large and expensive
External forceps method[21,22]	+	-	+	Regrasping, no need of assistant to hold the forceps	Care of mucosal damage
Internal traction method[23-25]	-	-	-	Easy	Roll back of mucosa
Spring-assisted ESD[26]	-	-	-	Easy	
Double-channel-scope method[28]	+	+	+	Regrasping	Synchronous movement of forceps and scope
R-scope[29-31]	+	+	+	Regrasping, swing of knife	Thicker and heavier scope, synchronous movement of forceps and scope
Outerroute method[33-38]	+	+	+	Regrasping	Synchronous movement of forceps and scope, small distance between forceps and knife
Double-scope method[10]	+	+	+	Regrasping	Interference of scopes, two light sources, double manpower
Morita[39]	+	+	+	Regrasping, a little interference of scopes	Thicher overtube, two light sources, double manpower
Higuchi[40]	+	+	+	Regrasping, one light source	Interference of scopes, double manpower
Robot-assisted method[42-44]	+	+	+	Regrasping	More complicated, no response of hemostasis
ESD with traction in colon and rectum					
Sinker-assisted method[45]	-	-	+	Easy	Retreival of scope
External forceps method[46]	+	-	+	Regrasping	Retreival of scope, only rectum
Internal traction method[47-50]	-	-	-	Easy	
Outerroute method[51]	+	+	+	Regrasping	Synchronous movement of forceps and scope
Double-scope method[52,53]	+	+	+	Regrasping	Two light sources and double manpower, interference of t scopes, lesions in only sigmoid colon and rectum
Fusaroli[54]	+	+	+	Regrasping, much cheaper, one light source	interference of scopes, lesions in only sigmoid colon and rectum
Endoscopic surgical platform[55]	+	+	+	Regrasping, freedom offering surgical triangulation	more complicated configuration with fixed instruments, only rectum

ESD: Endoscopic submucosal dissection.

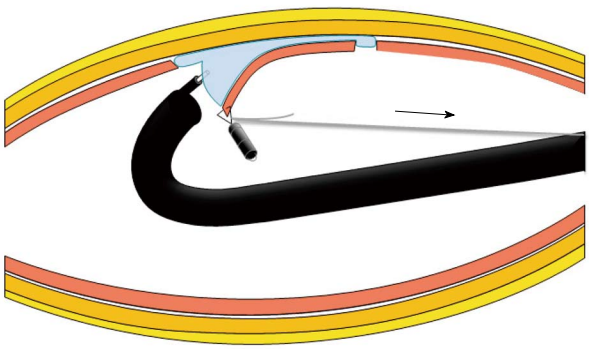

Figure 1 Schema of clip-with-line method.

set of two clips connected by a rubber ring or a nylon line is used. The first clip connected by a rubber ring or nylon line is attached at the target part after circumferential incision. Parra-Blanco *et al*[23] reported the clip-band method. Matsumoto *et al*[24,25] reported on a new traction device called "medical ring". This device is mounted by connecting it to a hemoclip with 3-0 silk. The second clip is attached at the opposite sides of the lesions (Figure 6A). This method pulls up the lesion and opens the resection margin. Since lesions roll back, the traction direction and elevation of the submucosal layer is not sometimes sufficient. Sakurazawa *et al*[26] reported on spring-assisted ESD (Figure 6B). One end of the stainless-steel spring device (length 20 mm) is fitted with a polyurethane loop and the other end is fitted with a clip, which was attached to the opposite side. The spring lengthens by more than 10 fold in this range. However, the spring device is made of stainless steel, and its safety within the intestinal tract has not been established. Chen *et al*[27] reported on the nylon line method using 2 hemoclips. However, this method might not be applicable for neoplasms in the py-

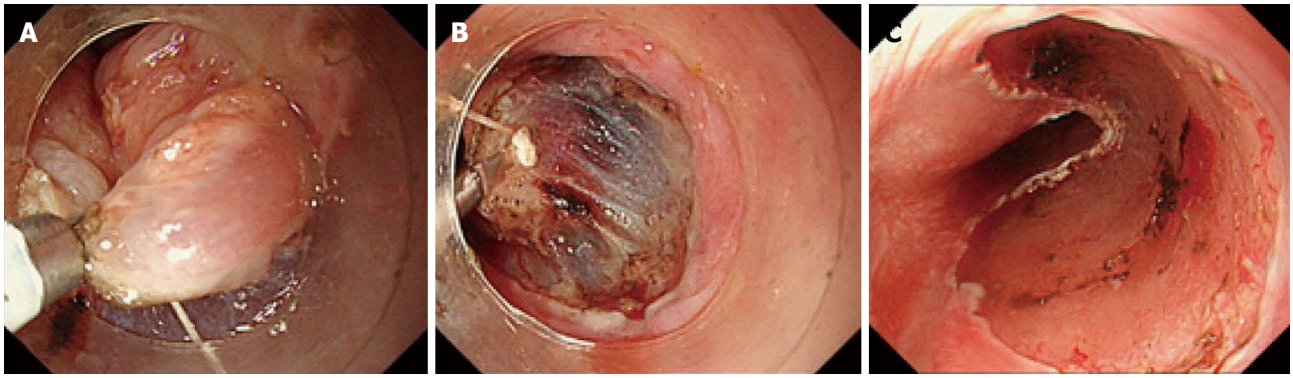

Figure 2 Clip-with-line method. A: Submucosal side of the target lesion in the esophagus was grasped using clip tied to long silk line; B: When the line was pulled very gently, submucosal layer was elevated; C: Lesion was dissected *en bloc*.

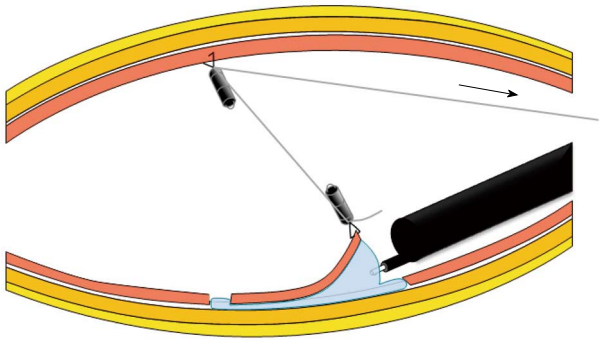

Figure 3 Schema of pulley method. The first clip with the line can be pulled to the anal side with the second clip, which is fixed at the opposite side.

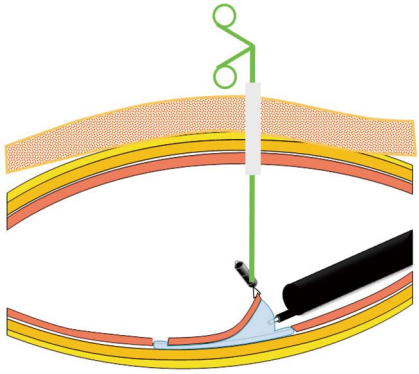

Figure 4 Schema of Percutaneous-traction method. A small snare is introduced into the gastric lumen through a gastric port to grasp and pull the lesions.

lorus or cardia, where space is limited, and control of the traction power is sometimes difficult.

Double-channel-scope method

A pair of grasping forceps inserted into a channel of a double-channel scope can create traction during ESD. Ishigooka *et al*[28] reported on endoscopic resection with injection of hypertonic saline epinephrine using a double-channel scope (S-ERHSE). Yonezawa *et al*[29] reported on ESD using an R-scope, which has two movable instrument channels: one moves a pair of grasping forceps vertically for lesions with traction and the other swings a cutting knife horizontally for dissection (Figure 7). Neuhaus *et al*[30] and Lee *et al*[31] also reported on this method using the R-scope, which facilitated ESD of large gastric areas. Even though the concept was good, the endoscope required a significant learning period to enable proficiency in its use. The forceps moves synchronously with the scope, therefore, it is sometimes difficult to control the traction direction. Hijikata *et al*[32] reported on ESD using the outer sheath of an injection needle. The bottom of the dissected mucosal layer is pushed and lifted up using the injection sheath through one channel to reveal the submucosal layer and ensure adequate traction, and submucosal dissection was conducted by an IT-knife through the other channel. However, a double-channel scope is thicker, heavier, and more difficult to manipulate than a single-channel endoscope. Moreover, since the grasping forceps or the outer sheath is inserted through the endoscope, it moves synchronously with the endoscope, which sometimes makes it difficult to control the traction direction and to cut the submucosal layer of larger lesions.

Outerroute method

Motohashi *et al*[33,34] reported on ESD using the Impact Shooter®, which is mounted on the scope (Figure 8). The mucosa was hold with the forceps through the channel which was connected to the Impact Shooter®, and the submucosal tissue was dissected with the hook knife. However, the forceps moves synchronously with the endoscope and the distance between forceps and knife is not sufficient; therefore it is sometimes difficult to control the traction direction. Okamoto *et al*[35] and Tsao *et al*[36] reported on ESD using a clip with a nylon suture through a thin tube. The plastic sheath allows the endoscope to be easily maneuvered without interrupting the traction. Ohata *et al*[37] reported ESD using a biopsy forceps, which is straight when closed and curved when opened. It was inserted a long straw tube which was mounted on an overtube, and the edge of the targeted lesion was grasped and lift up. Teoh *et al*[38] reported on

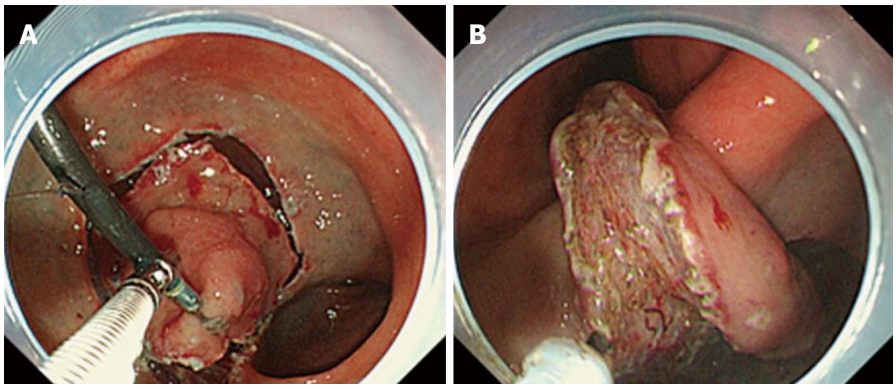

Figure 5 Endoscopic submucosal dissection using external forceps. A: External grasping was anchored at distal margin of lesion in the lesser curvature of the antrum under control of endoscope and second grasping forceps; B: With gentle oral traction applied with external grasping forceps, submucosal layer was dissected in retroversion from aboral side.

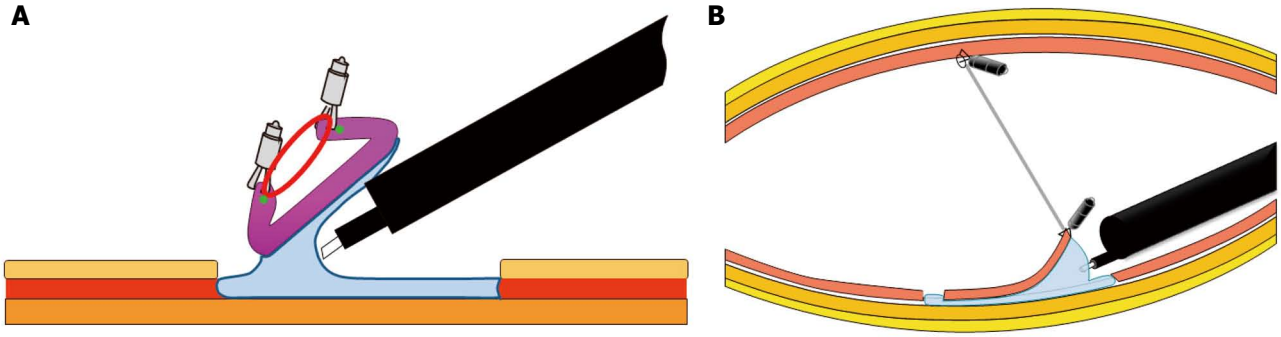

Figure 6 Schema of Internal traction method. A: The second clip is attached at the opposite sides of the lesions; B: The second clip is attached at the opposite sides of the stomach.

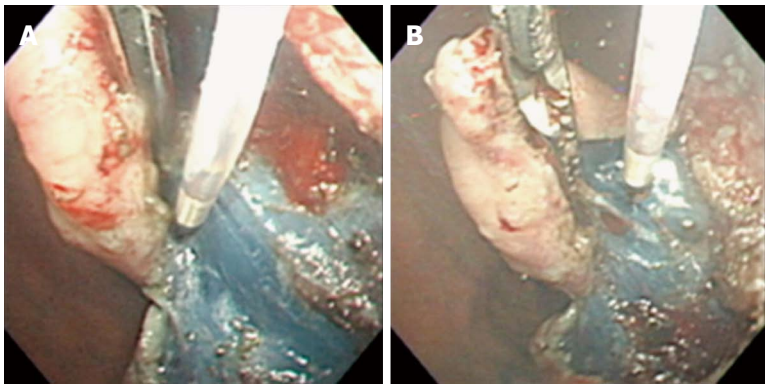

Figure 7 Endoscopic submucosal dissection using double-channel R-scope. A: R-scope has two movable instrument channels: one moves grasping forceps vertically for lesion with traction and other swings cutting knife horizontally for dissection; B Cutting knife was horizontally swung.

ESD using the Endolifter®, which consists of a retractable grasping forceps attached to a transparent cap by a hinge that allows simultaneous grasping, retracting, and lifting of the mucosa. However, these methods reduce the sideway movements of the endoscope due to retraction at a fixed point by the forceps, this in turn limits the maneuverability of the endoscope. The visual field is limited due to masking of the dissected part of the mucosa for large lesions.

Double-scope method

Since Hirao *et al*[10] reported on an EMR procedure using double endoscopes; several methods using a second thin endoscope have also been reported. The traction direction can be controlled easily with the double-scope method (Figure 9). However, the second scope sometimes limits the maneuverability of the main scope because of their combined diameter. Moreover, this method requires two light sources and more than

Figure 8 Schema of outerroute method.

two endoscopists and two assistants. Morita *et al*[39] described a double-endoscope method, which requires two light sources and a specially designed overtube with two channels to prevent interaction between two endoscopes. However, the overtube is thicker than the usual one. Higuchi *et al*[40] reported on another method without an overtube, which requires only one light source that can be transferred between two endoscopes, eliminating the problem of optical interference. After circumferential incision, the main scope is left in the stomach, and the light source is removed and attached to the thin endoscope. The thin endoscope is inserted along the main endoscope, and the lesion is grasped along its margin using grasping forceps. Thereafter, the light source is removed from the thin endoscope and reattached to the main endoscope, and submucosal dissection is done. However, the disadvantage is the same as the double scope method except for only requiring one light source. A thin trans-nasal endoscope-assisted ESD has been reported by Ahn *et al*[41]. This method has disadvantages, including nasal bleeding due to trans-nasal access, invasion due to double endoscopes, need for two endoscopists, and temporary hindrance of movement between endoscopes.

Robot-assisted method

Ho *et al*[42], Wang *et al*[43], and Phee *et al*[44] reported on ESD using a Master and slave trans-luminal endoscopic robot (MASTER). The MASTER consists of three major components: a master robotic controller, a telesurgical workstation, and a slave manipulator. The system is designed to work with a therapeutic endoscope with two operating channels. The master controller is the human-machine interface that controls the slave manipulator, a unilateral electromechanical device that responds to the operator's input and drives the end-effectors, grasper, and monopolar electrocautery hook. This method is similar to laparoscopic surgery. However, the disadvantage of the MASTER is its more complicated configuration with fixed instruments. If massive bleeding from a resected site occurs, it is necessary to change the therapeutic endoscope to a conventional endoscope to conduct hemostasis using hemoclips or hemostatic forceps.

ESD WITH TRACTION IN COLON AND RECTUM

ESD using traction for lesions on the colon and rectum is similar to that for lesions on the UGI tract. However, the lumen in the colon and rectum is narrow and bending. Moreover, for lesions in the proximal colon, reinsertion after retrieval of the endoscope is more time-consuming in some methods compared to that for lesions in the UGI tract. Therefore, lesions in only the rectum or sigmoid colon are indicated in some methods.

Sinker-assisted method

Saito *et al*[45] reported on sinker-assisted ESD for colorectal cancer. The sinker system is composed of a metallic clip attached to a 1-g sinker by a short nylon line. The metallic clip is attached to a target site at the edge of the exfoliated mucosa. The traction direction is controlled using gravity by changing the position of the body. A limitation of this method is the necessity of retrieving the scope to set up the sinker system.

External forceps method

Imaeda *et al*[46] reported on ESD using external biopsy forceps that are bendable (Figure 10). This procedure is similar to ESD using external grasping forceps for EGC[21,22]. The external bendable forceps was introduced with the help of the grasping forceps. After the external forceps was anchored at the anal margin of the lesion, with bending and gentle anal traction applied with the forceps, the lesion was elevated. However, it is used only for rectal cancers because of the difficulty in inserting and controlling the forceps in the colon.

Internal traction method

Sakamoto *et al*[47,48] reported on ESD using a S-O clip (Sakamoto and Osada clip). The S-O clip consists of a metal clip attached to the end of a spring or a rubber strip, its other end of which a double nylon loop is connected to. A spring S-O clip is attached to the edge of the exfoliated mucosa and a regular clip is used to grasp the distal nylon loop and applied to the colon wall opposite the lesion. Osada *et al*[49] also reported on ESD using a loop-attached rubber band, which consists of a circular rubber band connected to many nylon loops. Tomiki *et al*[50] reported on ESD using latex band traction. These methods are easy, safe, and noninvasive, and the instrument can be used at any location.

Outerroute method

Okamoto *et al*[51] reported on ESD using a clip with a nylon suture through a thin tube. This procedure is similar to ESD using a clip with a nylon suture through a thin tube for EGC[35]. However, this method needs a single balloon overtube, which enables the endoscope to be retrieved and inserted to set up the devices. The forceps moves synchronously with the endoscope and the distance between forceps and knife is not sufficient, therefore, this method limits the maneuverability of the endoscope. The visual field is limited due to masking of the dissected part of the mucosa for large lesions.

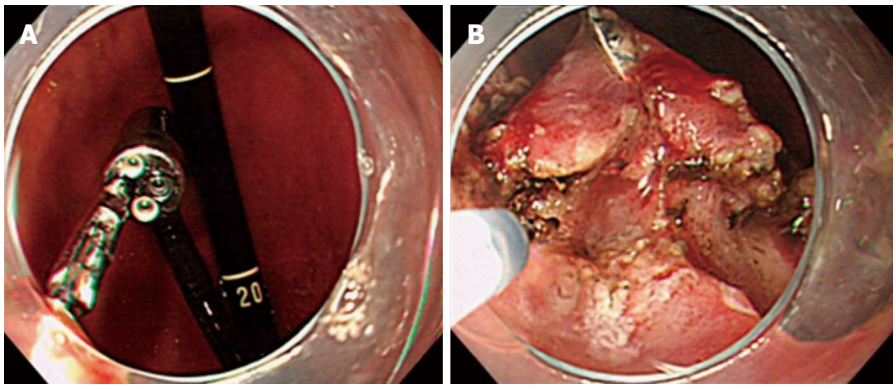

Figure 9 Endoscopic submucosal dissection using double-endoscopes. A: Lesion was grasped and lifted using grasping forceps through thin endoscope; B Submucosal dissection was done using needle knife through main scope.

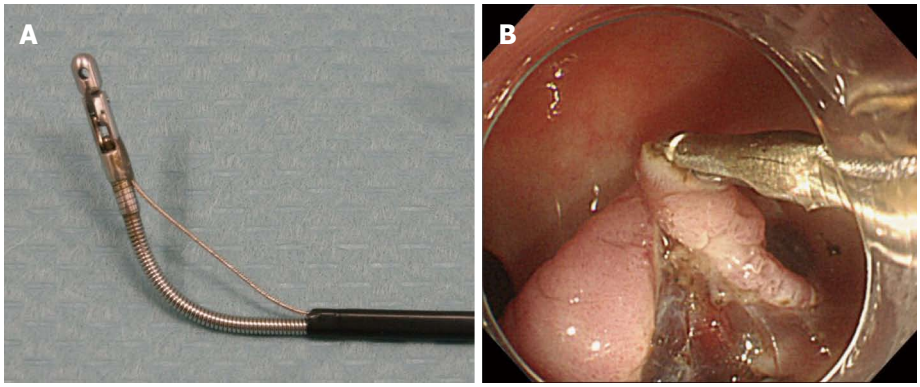

Figure 10 Endoscopic submucosal dissection using external forceps. A: Bendable biopsy forceps; B: Bending forceps and traction applied using forceps elevated lesion and widened submucosal layer.

Double-scope method

Uraoka *et al*[52,53] reported on a double-scope method for large colorectal tumors. An endoclip is attached to the edge at the exfoliated mucosa, a second thin endoscope is then inserted into the lumen followed by removal of the primary endoscope. A snare is used to grasp the positioned endoclip and pull the lesion away from the muscle layer. Once again, the primary endoscope is inserted to the location of the lesion. However, this method is limited to the rectum and rectosigmoid colon because of the difficulty in intubating the second endoscope to the oral side of the distal sigmoid colon. It requires a second endoscopist to operate the traction system. It also may be difficult for treating larger lesions, like the circumferential ones because of insufficient space to maintain the necessary cutting line view provided by the traction system. Fusaroli *et al*[54] reported on a double-scope method using a prototype blind multi-bending thin probe with a working channel of 2.8 mm. It is much cheaper (when on the market) and more resistant to shear stress than a pediatric scope. However, it is limited to treating lesion on the rectum or sigmoid colon. Two endoscopists and three nurses (one for care of the patient, one for handling accessories for main endoscope and one for handling accessories for the second endoscope) are required.

Endoscopic surgical platform

Diana *et al*[55] reported on ESD using an endoscopic surgical platform, the Anubiscope®, equipped with two working channels for surgical instruments with four degrees of freedom offering surgical triangulation and ESD using a robotic version of the Anubiscope®. However, it is limited to treating lesion on the rectum, and is a more complicated configuration with fixed instruments.

PERSPECTIVES FOR FUTURE

Although many kinds of ESD methods with traction have been reported, each method has not only some advantages but also the other disadvantages. Some methods require retrieving the scope to set up devices, others are limited to lesions in certain areas, directions and tension of traction, and still others are somewhat complicated and invasive. If each knife or a grasping forceps be moved independently, as in surgery, and the direction and tension of traction can be controlled at will, ESD with traction might become easier and more flexible. A grasping forceps with flexible bending function, which is thinner than an ultrathin endoscope, may make ESD with traction easier.

If robotic endoscopy, which enables ESD with traction, advances in technology in the near future, it may make ESD easier, may approach to the lesions in any area regardless of gastric movement due to respiration, and may also enable endoscopic hemostasis.

CONCLUSION

Simple and flexible methods with traction can make ESD easier and safer. In the near future, simple, noninvasive, and effective ESD with traction is expected to be developed and become established as a standard treatment for superficial gastrointestinal neoplasias worldwide.

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Laparoscopic management of gastric gastrointestinal stromal tumors

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most frequent gastrointestinal tumors of mesodermal origin. Gastric GISTs represent approximately 70% of all gastrointestinal GISTs. The only curative option is surgical resection. Many surgical groups have shown good results with the laparoscopic approach. There have not been any randomized controlled trials comparing the open *vs* laparoscopic approach, and all recommendations have been based on observational studies. The experience obtained from gastric laparoscopic surgery during recent decades and the development of specific devices have allowed the treatment of most gastric GISTs through the laparoscopic approach.

Key words: Gastrointestinal stromal tumors; Laparoscopy; Surgery; Stomach; Gastrectomy

Core tip: Gastrointestinal stromal tumors (GISTs) are the most frequent gastrointestinal tumors of mesodermal origin. Gastric GISTs represent approximately 70% of all gastrointestinal GISTs. The only curative option is surgical resection. Many surgical groups have shown good results with the laparoscopic approach. There have not been any randomized controlled trials comparing the open *vs* laparoscopic approach, and all recommendations have been based on observational studies. The experience obtained from gastric laparoscopic surgery during recent decades and the development of specific devices have allowed the treatment of most gastric GISTs through the laparoscopic approach.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most frequent gastrointestinal tumors of mesodermal origin[1], and gastric GISTs represent approximately 70% of all gastrointestinal GISTs[2]. These tumors are derived from the interstitial cells of Cajal[3], and have been shown to harbor gain of function mutations in the cell-surface KIT receptor in approximately 90% or in the platelet-derived growth factor receptor α (PDGFRA) in 8%[4].

Most tumors are limited to the primary organ, and less than 2% of tumors present lymph node metastasis. GISTs can also metastasize to the peritoneum and infrequently present hematogenous metastasis to other intra-abdominal viscera, lung, pleura, bone and brain[5].

Most patients are asymptomatic; the tumors are usually found as an incidental finding in 4%-39% of cases[6-11]. In most surgical series, the most frequent symptoms are gastrointestinal bleeding (14%-68%), abdominal pain (16.1%-45%), abdominal mass (3.3%-21%), early

satiety (36%), anemia (19.4%-77%), weight loss (11%), bowel obstruction (3.6%), liver metastasis (3.6%), dyspeptic symptoms (9.7%) and dysphagia (9%)[6-10]. There is a clear relationship between tumor size and symptoms, smaller tumores are generally asymptomatic[4].

The diagnosis is usually made by endoscopy or abdominal imaging. During endoscopy, it is possible to see gastric lumen narrowing associated with normal protruded mucosa, although in larger tumors, the mucosa can show ulcers due to local ischemia[12,13]. The ideal method for diagnosis is endoscopic ultrasonography (EUS), which can define the size, vascular pattern and form of the tumor and differentiate between an extraluminal compression and a submucous growth. GISTs are hypoechoic tumors located at the fourth layer, although some reports have shown tumors located at the third layer. However, the imaging of these tumors is not sensitive (43%), which necessitates histologic evaluation. EUS also helps guide fine needle aspiration biopsies, showing better performance than biopsies under normal endoscopy[12]. The sensitivity of FNAB guided by EUS increases by 10% if a pathologist makes an immediate examination of the adequacy of the sample[13]. In some series, preoperative diagnosis was only possible 52.3%[7].

Computed tomography (CT) is necessary for preoperative stratification. CT can usually show intra- or extraluminal tumors with different morphologic patterns according to size. Larger tumors can show irregular margins and heterogeneous internal density, and if the diameter is larger than 6 cm, the tumors are usually accompanied by central necrosis. Magnetic resonance imaging (MRI) is recommended in cases of simultaneous liver metastasis because of the possibility of conducting a combined resection. PET-CT can be useful in patients with undetermined findings on CT or MRI[14]. However, there is not a good correlation between imaging findings and malignancy[15].

A differential diagnosis with other submucous tumors such as leiomyoma, leiomyosarcoma, schwannoma, granular cell tumors, heterotopic pancreatic tissue, lipoma, neurofibroma, Kaposi tumors and non-functional adrenal tumors should be performed[16,17]. Immunohistochemistry for GIST detection is very useful and shows positivity for CD117 (95% of GISTs)[16]. Only 2% are usually related to PDGFRA mutations[16,18]. Other helpful tests are CD34 that is positive in 70% of the cases and vimentin[16].

SURGICAL TREATMENT

The only curative option is surgical resection, which can be offered to patients with good functional status and non-metastatic resectable tumors, although in some cases, a metastasis resection surgery can be performed in association with resection of the primary tumor[19]. Surgical principles for resection include total extracapsular resection, avoiding tumor fracture or bleeding, which are associated with recurrence and peritoneal sarcomatosis[20]. There are no recommended margins, because microscopic margins status doesn´t correlate with survival as does the mitotic count and tumor size. Wedge resection is a good option for tumors located in the anterior wall or greater curve. For tumors located at the antrum wedge resection can produce a stenosis, so formal gastric resections are favored. Wider margins have not shown any oncologic advantage[21], and lymph node dissection has not been indicated[22]. The National Comprehensive Cancer Network (NCCN) guidelines suggest that tumors smaller than 1 cm that do not fulfill high risk endosonographic criteria (irregular borders, cystic spaces, ulcer of echogenic heterogeneous focus) can be observed during endoscopic follow-up at each 6-12-mo interval[23]. Most larger tumors need adjuvant treatment with imatinib mesylate to avoid recurrence[2].

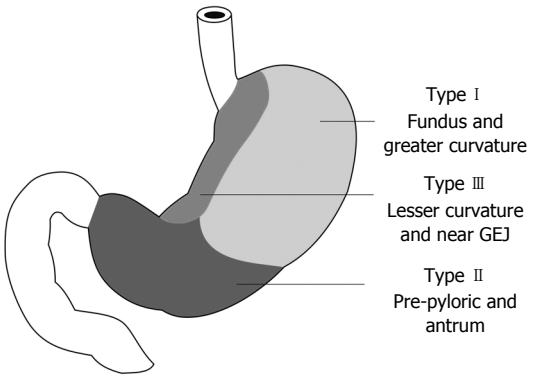

Figure 1 Surgical approach according to gastrointestinal stromal tumor localization.

LAPAROSCOPIC TREATMENT

Open surgical resection was the standard of treatment until two decades ago. Many surgical groups have shown good results with the laparoscopic approach. Although NCCN guidelines suggest that laparoscopic resection is indicated in tumors less than 2 cm, many surgeons have reported a safe excision of tumors > 5 cm and other up to 10 cm[24-26]. Lukaszczry and Pretez in 1992 were the first to report a successful laparoscopic resection of a gastric GIST[27].

The laparoscopic techniques can be divided into different subtypes: transgastric resections, endoscopy-assisted laparoscopic resections, wedge resections, partial gastrectomy and hand-assisted laparoscopic resections[24]. The surgical approach depends on tumor size and location (Figure 1). Privette *et al*[25] proposed a classification system based on tumor location as a guideline to choose the best surgical approach. Trocars and operating tables are organized in a similar manner to any other hiatus procedures, with the surgeon located between the legs. A 12-15 mmHg pneumoperitoneum is established, and a 30° camera and a liver retractor are useful. Before resection, it is mandatory to review the abdominal cavity to rule out peritoneum or liver metastasis. If the surgeons

Table 1 Non-comparative series of laparoscopic resection of gastric gastrointestinal stromal tumor

Ref.	*n*	Age (yr)	Tumor size	Tumor localization	Type of surgery	OR time (min)	Notes	Complications/ conversions	Follow-up (mo)
Privette *et al*[25]	12	60.5	5.2 cm PG 4.6 cm TransG 5.5 cm DG	5 Fundus or greater curvature 3 Prepyloric or antral 5 Lesser curvature	5 PG × Lap 3 DG × Lap 5 TransG × Lap	PG 180 (122-262) DG: 322 (256-340) TransG: 236 (202-265)	9/12 GIST 1 Schwannoma 2 Leiomiomas LOS: GP: 3.4 GD: 8.3 GT: 3.3	16.6% complication 1 Enterotomy 1 GI Bleeding No conversions	Only specified for 5 pts
Sexton *et al*[32]	61	59.1 ± 19	3.8 ± 1.8 AR: 229.7 NAR 140.9	Fundus 19 Antrum 18 Body 17 GE junction 7 Pylorus 2	PG 52 DG 4 TotGas 3 TransG 3	151.9 ± 67.3	LOS: 3.9 ±2 LOS AR: 3.9, NAR: 4.1	16.4% complication No conversions 1 POP death	15 (0-103) 3 recurrences
Berindoague *et al*[9]	22	66.7	5.6 (2.5-12.5)	Upper third 6 Middle third 7 Lower third 10	GP 13 1 LAP-HA TotGas 1 LAP TotGast 1 LAP-HA GD 1 TransG	NR	18/22 GIST 1 Adenomyoma 1 Hamartoma 1 Plasmocytoma 1 Parasitic Tumor (anisakis) LOS 6 (4-32)	18.2% complication 3 Delayed gastric emptying 1 Intestinal Obstruction 2 Conversions (9.1%)	32 m (1-72) 1 recurrence
De Vogelaere *et al*[24]	31	63.8	4.4 (0.4-11)	Anterior gastric wall 23 Others not specified	31 PG	99	LOS 8.5	3.2% Complication 1 POP Bleeding	56.3 No recurrences
Hwang *et al*[10]	63	52.8	3.5 GE Junction 3.4 Prepyloric Size of other tumor not specified	7 GE junction Upper third 22 Middle third 11 Lower third 19 4 Prepyloric	3 DG 37 PG 23 TransG (5 Enucleations)	86.1 ± 43.7	LOS 5.3 ± 1 1.8 41 GIST 8 Leiomyoma 4 Carcinoids 1 Liposarcoma 6 Heterotopic Pancreas 2 Hyperplastic Polyps 1 Parasitic Infection	4.7% Complication 1 Staple line bleeding 1 SSI 1 Staple line dehiscence	14.9 (2-42) No recurrences
Novitsky *et al*[26]	50	60 ± 13	4.4 ± 2.0 cm	GE Junction 8 Cardias 9 Anterior Wall 10 Posterior Wall 4 Greater Curvature 6 Lesser Curvature 3 Antrum 4 Prepyloric 6	TotGas 1 DG 2 PG 40 LAP/END 4 LAP-HA 3	135 ± 56	LOS 3.8 ± 1.6	8% 4 Minor complications	36 (4-84) 4 recurrences
Lai *et al*[2]	28	56.9 ± 12.4	3.4 ± 1.6	Upper third 13 Middle third 8 Lower third 7	28 PG	189.6 ± 79.5 Stapled 194.3 ± 50.5 Hand-Sewn	LOS 6.7 ± 1.8	3.5% conversion	43.3 ± 23.5 No recurrences
Choi *et al*[36]	23	59.7 ± 8.3	4.2 ±2.1	Upper third 13 Middle third 5 Lower third 5	23 PG	104.3	LOS 5.2 ± 2.3	4.3% complication 1 Delayed gastric emptying No conversions	61 (7-98)
Nguyen *et al*[22]	28	65	4.6 (0.4-11.5)	LAP PG 22 Subtotal Gastrectomy 3 OS (Converted) : TotGas 1 Intraluminal excision 1 1 Not specified	23 GP × LAP 3 GD × LAP 1 GT × LAP 1 TotGas × CA (converted)	143 (46-336) This includes Small Bowel GIST resections. No data only on gastric resections	LOS 4 (1-50 d)	9% complications 11% 3 conversions Mortality 1 POP death This includes Small Bowel GIST resections. No data only on gastric resections	NS
Huguet *et al*[37]	33	68	3.9 (0.5-10.5),	GE Junction 5 Body 24 Antrum 4	PG 29 LAP-HA PG 4	124 (30-253)	LOS 3 (1-40)	9% complications 2 POP Bleeding 1 SSI 6% conversions	13 (3-64) No recurrences

Ronellenfitsch *et al*[38]	17	56 (43-79)	2.9 (0.8-6)	11 Not specified 6 Antrum	17 PG	130 (80-201)	LOS 7 (5-95)	11.8% Complications: Staple leaks 5% conversion (peritoneal adhesions)	18 (1-53) No recurrences
Tagaya *et al*[39]	15	65.3 (52-75 years)	TransG 2.9 (1.7-6.5) GP 3.9 (1.2-8)	TransG: Upper third 4 Middle third 1 Lower third 1 PG: Greater curvature 2 Lesser curvature 1 Anterior wall 2 Middle third Ant wall 1 Middle Third Post wall 1	TransG 8 PG 7	TransG:168 (132-211) PG: 121 (60-190)	LOS TransG: 8.8 (7-12) LOS PG: 9.6 (7-14)	No complications	After final Pathology only 9 tumors were GIST TransG 18-73 PG: 6-122 No recurrences

GLA: Gasless laparoscopy-assisted; PG: Wedge Resection or Partial Gastrectomy; DG: Distal Gastrectomy; TransG: Transgastric Gastrectomies; TotGas: Total Gastrectomy; OS: Open surgery; AR: Anatomic resections; NAR: Non-anatomic resections; LOS: Length of stay; NS: Not specified; LAP/END: Laparoendoscopic resection; LAP-HA: Laparoscopic hand-assisted; RG: Remnant Gastrectomy; Prox Gas: Proximal Gastrectomy; SSI: Surgical site infection.

suspect solid organ metastasis, the use of intraoperative ultrasound with biopsy can help in the operative decision. Assistance by endoscopy during the surgical procedure is useful for locating the tumor and guiding resection, and staining with ink could help delineate the resection margins.

Tumors located at the fundus and at the anterior and posterior walls can be resected by partial gastrectomy or wedge resection. In cases of small tumors, the greater curve is mobilized, ligating the gastroepiploic vessels with an ultrasonic scalpel or a thermal device. The gastric wall is elevated with sutures placed in the seromuscular layer around the tumor to obtain a complete resection with a linear mechanical stapler, guaranteeing macroscopic margins. In cases of larger tumors, the gastric wall is directly opened and the tumor is resected, maintaining a free margin with a late direct closure using a continuous suture. In cases where tumors are located in the posterior wall, an anterior gastrotomy is made exactly above the tumor, usually assisted by endoscopy. The tumor is resected by the techniques described, with a late closure of the anterior wall with a continuous suture[11,26].

For tumors located at the antrum or at the prepyloric area, partial gastrectomy is recommended due to the high risk of stenosis and delayed stomach emptying when wedge resections are used. In these cases, the greater and lesser curves are dissected to obtain retrogastric access. The duodenum is sectioned just distal to the pylorus with a linear mechanical stapler, and the proximal section is also made with a mechanical stapler; this is usually assisted by endoscopy. Finally, a Roux-en-Y anastomosis is made[25].

Tumors located at the esophagogastric junction are infrequent and represent less than 5% of all tumors. Some authors have recommended enucleation of these tumors based on the high morbidity (6%-24%) and mortality (0%-1.5%) with classical resections and due to the lack of advantage in prognosis and survival[28]. However, the best surgical approach is still debated[29]. The enucleation is made through an anterior gastrotomy, and in these cases, a submucous infiltration with epinephrine is recommended to avoid bleeding and perforation. The use of devices such as an ultrasonic scalpel or an electrocautery has been recommended[10,28].

Some authors have varied the surgical technique using transgastric trocars and endoscopy-assisted insufflation. In these cases, smaller tumors can even be extracted by the mouth using endoscopy[25]. For larger tumors, other authors have suggested a hand-assisted technique because it allows for better exploration and easier handling and dissection of the tumor[12,13]. Others have also shown good results with the single-port approach or dissections without insufflation[8]. In all cases, the use of a bag is recommended for the extraction of the tumor to avoid recurrence and metastasis at the port insertion sites[30,31].

Until now, there have not been any randomized controlled trials comparing the open *vs* laparoscopic approach, and all recommendations have been based on observational studies. Actual recommendations are based on outcomes related to surgical technique (intact specimen, free margins) and prognosis (operative complications, recurrence, cancer free survival)[32] reported from these observational studies. Tables 1 and 2 show the results of comparative and non-comparative published series.

Recently, Koh *et al*[33] published a systematic review of eleven observational studies comparing laparoscopic *vs* open resection with evaluation of short and long term

Table 2 Comparative series of laparoscopic resection of gastric gastrointestinal stromal tumor

Ref.	*n*	Age	Tumor size	Tumor localization	Type of surgery	OR time (min)	Notes	Complications/ conversions	Follow-up (mo)
Wu *et al*[8]	28	61.6 GLA 60.7 CA	2.6 ± 1 1.8 GLA 2.5 ± 1.0 CA	Anterior fundus: 5 GLA 5 CA Posterior fundus: 6 GLA 2 CA Anterior body: 3 GLA 3 CA Posterior Body: 1 GLA 3 CA	15 GLA 13 OS All were Wedge Resections	GLA 129 ± 36.1 CA 110.8 ± 38.1	GLA Less POP Pain during the first 3 d Earlier oral intake Less LOS 5.8 *vs* 7.2 días	7.1% complication 1 OS Ileus 1 Enterotomy during GLA corrected during LAP	NR
Catena *et al*[7]	21	50.1	4.5 ± 2.0	Body 16 Antrum 4 Fundus 1	21 PG	151 ± 56	LOS 4.8 ± 1.6	No intraoperative complications	35 (5-58)
	25	54.6	6.2 ± 1.9	Body 17 Antrum 6 Fundus 2	25 OS (PG)	134 ± 33	LOS 7.1 ± 1.2	No differences in complications	91 (80-136) 1 recurrence
Melstrom *et al*[31]	46 17 LAP 29 OS	62 Lap 60 OS	OS 6.39 82.1-10) LAP 4.27 (1.5-9.1)	Lap: Upper third 6 Middle third 10 NS 1 OS: Upper third 6 Lower third 22 NS 1	17 PG 24 PG × OS 4 DG × OS 1 TotGas × OS	Lap 135 OS 157	LOS: OS 6.25 LAP 2.68 I	Complications OS: 13.8% LAP: 11.8% 6% conversion	OS 59 4 recurrences LAP 32 No Recurrences
De Vogelaere *et al*[11]	53		Total 5.9					LAP : 2.7% 1 Pulmonary Embolism	Lap 83
	37 LAP	LAP 63.7 ± 15.4	LAP 5.6	Not specified	Not specified	LAP 48.5 ± 16	LOS Lap 7		No Recurrences LAP
	16 OS	OS 63.7 ± 10.7	OS 7.5	Not specified	Not specified	OS 155 ± 48.1	LOS OS 14	OS 18.7% complications: Pneumonia 1 Anastomotic Ulcer 1 Fistula 1	OS 71 6 recurrences CA
Karakousis *et al*[40]	80	68	OS 4.3 (2-9)	OS : Fundus 7	OS 39 PG 1 DG	OS 89	LOS: LAP 4 OS 7	Complications OS 25% LAP 14%	LAP 28 (0.3-70 m) Recurrences 1 LAP
	OS 40		LAP 3.6 (0-7-7.8)	Body/antrum 32 Pylorus 1 Lesser curvature 12	LAP 40 PG	LAP 96		32.5% Conversions	OS 43 (0.1-139) Recurrences 1 OS
	LAP 40			LAP: Fundus 3 Body/antrum 37 Pylorus 0 Lesser curvature 10					
Kim *et al*[41]	104	59.8 ± 10.5	5.1 ± 3.3	Upper third 61	Technique according to procedures was NS	LAP 91.1 ± 57 CA 165.8 ± 75.6	LOS LAP 4.6 ± 2.3 CA 9.8 ± 4.1	1% Complications 1 Delayed Gastric Emptying	49.3 (8.4-164.4) Recurrences 5 No Difference in recurrences between OS and LAP
	LAP 80			Middle third 24					
	OS 24			Lower third 19	99 PG 5 TotGas				
Silberhummer *et al*[21]	63 OS 41 LAP 22	62.3 ± 14.4	CA 5.8 ± 4.0 LAP 3.5 ± 1.4	Body 29 Antrum 18 Fundus 10 GE Junction 6	OS: PG 32 DG 5 RG 4 LAP 19 Tumorectomy 3 PG	135 ± 56	LOS LAP 7.8 (± 3.1) LOS CA 12.8 ± 5.0	4.7% complications: 1 Gastrocutaneous Fistula 1 Catheter Sepsis 1 POP Ileus LAP: 18.2% conversions	37 ± 27.9 Recurrences in 4 (7%)
Nishimura *et al*[42]	LAP 39	62	LAP 3.8 (0.8-7.3)	LAP: Upper third 19 Middle third 16 Lower third 4	LAP GP: 12 LAP-HA 17 TransG 10	LAP: 136 min OS: 115 min	NR	No Complications Conversion Rate 2.6%	LAP: 18.9 (2.6-96.4) Recurrences 4 LAP

	OS 28		OS: 4.2 (2.0-7.0)	OS Upper third 11 Middle third 11 Lower third 6	OS PG: 19 Prox Gas: 5 TotGas: 3 DG:1				OS: 31.2 (4.4-121.9) 1 Recurrence OS
Otani *et al*[43]	60 OS 22 LAP 38	59 (32-86)	4,25 (1.8-15.0)	Upper third 36 Middle third 20 Lower third 4	LAP: PG: 35 LAP-HA: LAP-HA PG 2 LAP-HA DG 1 OS: PG 11 ProxGas 9 DG 2	LAP 141 LAP-HA 188 CA 197	LOS LAP 7.2 *vs* 13.7 CA	3.3% complications: 1 Gastric Stenosis 1 Anastomotic Leak	53 mo 2 Recurrences

GLA: Gasless laparoscopy-assisted; PG: Wedge resection or partial gastrectomy; DG: Distal gastrectomy; TransG: Transgastric gastrectomies; TotGas: Total gastrectomy; OS: Open surgery; AR: Anatomic resections; NAR: Non-anatomic resections; LOS: Length of stay; NS: Not specified; LAP/END: Laparoendoscopic resection; LAP-HA: Laparoscopic hand-assisted; RG: Remnant gastrectomy; Prox Gas: Proximal gastrectomy; SSI: Surgical site infection.

outcomes. In their study, which included 381 patients in the laparoscopic group and 384 patients in the open group, the laparoscopic approach showed a lower frequency of minor complications (OR = 0.517; 95%CI: 0.277-0.965), lower length of stay [mean difference -3.421 d (-4.737 to -2.104)], shorter time to the initiation of oral diet [mean difference -1.887 d (-2.785 to -0.989)] and lower intraoperative bleeding [mean difference -86.508 mL (-141.184 to -31.831 mL)]. They could not find any statistically significant differences in reoperation rate, operative time, positive margins, local recurrence, cancer free survival and overall survival. However, comparisons showed that most high risk tumors were treated with open gastrectomy, introducing a selection bias.

The rate of conversion to open surgery is 0%-31%[11], and this cannot be considered a complication but rather an intraoperative decision to obtain better tumor control when the surgeon is faced with adverse intraoperative conditions.

Follow up

Follow-up is mandatory in all patients, even in the absence of malignancy. Patients should be reviewed every 3-6 mo during the first 5 years. An annual endoscopy and CT are recommended to rule out local recurrence[20]. The survival rate of patients with early tumors is greater than 90%[34]. A size larger than 10 cm, a high mitotic rate and intraoperative rupture are risk factors for recurrence[35].

CONCLUSION

The experience obtained from gastric laparoscopic surgery during recent decades and the development of specific devices have allowed the treatment of most gastric GISTs through the laparoscopic approach. As with all surgical techniques, the laparoscopic approach must be applied in select patients with particular characteristics based on functional status, tumor size, location and surgeons' experience. The case series presented in this review support laparoscopic resection as a safe and effective alternative, with similar rates of complications, but with lower pain and an early recovery. It is important to realize that tumor size by itself is not an adequate factor to contraindicate the laparoscopic approach and that other factors should be considered in the decision.

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ORIGINAL ARTICLE

Histology assessment of bipolar coagulation and argon plasma coagulation on digestive tract

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Abstract

AIM: To analyze the effect of bipolar electrocoagulation and argon plasma coagulation on fresh specimens of gastrointestinal tract.

METHODS: An experimental evaluation was performed at Hospital das Clinicas of the University of São Paulo, on 31 fresh surgical specimens using argon plasma coagulation and bipolar electrocoagulation at different time intervals. The depth of tissue damage was histopathologically analyzed by single senior pathologist unaware of the coagulation method and power setting applied. To analyze the results, the mucosa was divided in superficial mucosa (epithelial layer of the esophagus and superficial portion of the glandular layer of the stomach and colon) intermediate mucosa (until the lamina propria of the esophagus and until the bottom of the glandular layer of the stomach and colon) and muscularis mucosa. Necrosis involvement of the layers was compared in several combinations of power and time interval.

RESULTS: Involvement of the intermediate mucosa of the stomach and of the muscularis mucosa of the three organs was more frequent when higher amounts of energy were used with argon plasma. In the esophagus and in the colon, injury of the intermediate mucosa was frequent, even when small amounts of energy were used. The use of bipolar electrocoagulation resulted in more frequent involvement of the intermediate mucosa and of the muscularis mucosa of the esophagus and of the colon when higher amounts of energy were used. In the stomach, these involvements were rare. The risk of injury of the muscularis propria was significant only in the colon when argon plasma coagulation was employed.

CONCLUSION: Tissue damage after argon plasma coagulation is deeper than bipolar electrocoagulation. Both of them depend on the amount of energy used.

Key words: Argon plasma coagulation; Electrocoagulation; Gastrointestinal endoscopy; Surgical procedures; Endoscopic gastrointestinal; Mucous membrane/injuries

Core tip: The best way of applying heat to hollow digestive organs during thermal endoscopic therapy has not been clearly established so far. This study analyzes the histophathological effect of bipolar electrocoagulation and argon plasma coagulation on fresh surgical specimens of the digestive tract. Tissue damage after argon plasma coagulation is deeper than bipolar electrocoagulation. Both of them depends on the amount of energy used.

Garrido T, Baba ER, Wodak S, Sakai P, Cecconello I, Maluf-Filho F. Histology assessment of bipolar coagulation and argon plasma coagulation on digestive tract. *World J Gastrointest Endosc* 2014; 6(7): 304-311 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i7/304.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i7.304

INTRODUCTION

The association of diathermy to endoscopy has provided significant advances in endotherapy, which became a valuable alternative to traditional surgery and therapeutic procedure of choice in several conditions (*e.g.*, sphyncterotomy, polypectomy)[1-3]. Such a safe and cost-effective approach has justified the widespread of gastrointestinal endotherapy. However, reports of severe complications associated to endoscopic coagulation are common[4,5]. Pleural effusion, esophageal and colonic perforation and fistulae have followed argon plasma coagulation[6-8]. A case of colonic perforation has been associated to bipolar coagulation[9]. On the other hand, power setting and time interval of endoscopic coagulation can be very variable among authors[7,10-13]. The best way of applying heat to tissue has not been clearly established for hollow organs so far.

The aim of this study was to analyze the depth of coagulation necrosis caused by bipolar electrocoagulation and argon plasma coagulation on fresh gastrointestinal specimens, using different power settings and time intervals.

MATERIALS AND METHODS

Nine fresh surgical specimens of esophagus, 11 of stomach and 11 of colon were submitted to bipolar electrocoagulation and argon plasma coagulation. Surgical specimens of esophagus, stomach and colon, resected for neoplasic diseases were given to the author in the surgical room, right after the end of surgery. The specimens were kept in saline solution from the time of its removal until its preparation for thermal appliance (median of 3 h). Bipolar electrocoagulation was applied with power settings of 20 W and 50 W, during 1, 3, 5 and 10 s. A 454A Kairos - DNI Nevada Inc.® equipment and 7Fr QuickSilver-COOK® probes were used for bipolar electrocoagulation (Figure 1A). The specimens were also coagulated by argon plasma, with power settings of 50, 70 and 90 W, during 1, 3 and 5 s. An ICC 300 - ERBE® equipment and 7Fr GIT - ERBE® probes were used for argon plasma coagulation. The argon gas flow was set to 2l/min. The probe was kept up to 2 cm from the tissue surface, in an angle of 90°. In the esophagus, the combination of 20 W × 1s for bipolar electrocoagulation and 70 W power setting for argon plasma coagulation were not applied due to less available tissue (Figure 1B).

The depth of tissue damage was histopathologically analyzed by a single senior pathologist unaware of the coagulation method and power setting applied, with the help of an optic microscope (40 ×, 250 × and 400 ×). Citoplasmatic acidofilia, cellular picnosis and the presence of "ghost cells" were the histopathological parameters used to define cellular necrosis (Figure 2).

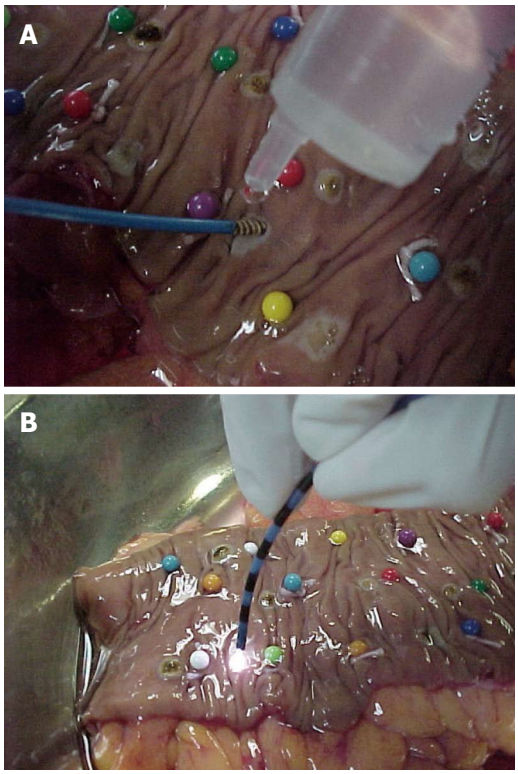

Figure 1 Colon specimen. A: Bipolar electrocoagulation of a colon specimen; B: Argon plasma coagulation of a colon specimen.

Necrosis involvement of the intermediate mucosa, the muscularis mucosa and the muscularis propria of the specimens was observed for the relevance of this stratification in clinical practice.

The intermediate mucosa was considered involved when necrosis was noted until the lamina propria of the esophagus or deep portion of the glandular layer of the stomach and colon. The muscularis mucosa was considered involved when necrosis was present through its whole extension. Muscularis propria was considered involved when any extension of necrosis was present. For both methods, necrosis involvement of the layers was compared in several combinations of power and time interval. Q-square and Fisher´s test were used for the statistical analysis and a level of significance < 5% was adopted.

RESULTS

Macroscopically, coagulated spots from both methods resulted in depressed whitish lesions to brownish ulcerations associated to blisters (Figure 3).

The frequency of involvement of the layers in different combinations of power setting and time interval, in both methods, is shown in Tables 1-6. Involvement of

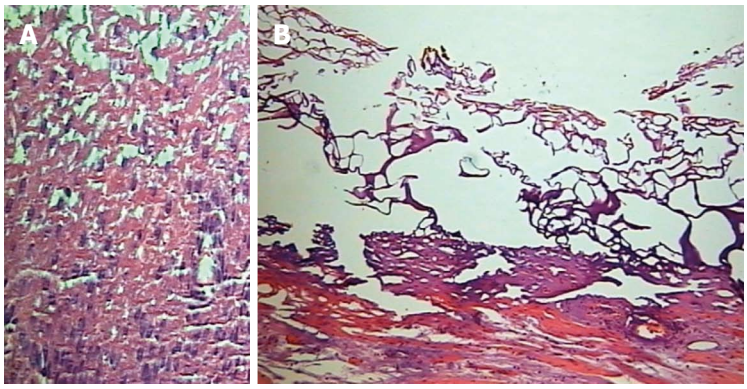

Figure 2 Cellular necrosis. A: "Ghost cells" [hematoxylin and eosin (HE), 250 ×]; B: Citoplasmatic acidofilia and cellular picnosis (HE, 400 ×).

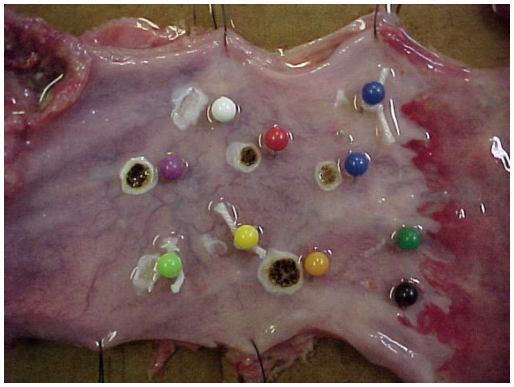

Figure 3 Macroscopic aspects of coagulated spots (both methods).

the intermediate mucosa of the stomach and of the muscularis mucosa of the three organs was more frequent when higher amounts of energy were used with argon plasma. In the esophagus and in the colon, injury of the intermediate mucosa was frequent, even when small amounts of energy were used. The use of bipolar electrocoagulation resulted in more frequent involvement of the intermediate mucosa and of the muscularis mucosa of the esophagus and of the colon when higher amounts of energy were used. In the stomach, these involvements were rare. The risk of injury of the muscularis propria was significant only in the colon when argon plasma coagulation was employed.

Figure 4 show the microscopic aspect of coagulated spots with different depths of coagulation necrosis.

DISCUSSION

The ideal way of applying thermal endoscopic methods to gastrointestinal wall should be deep enough to obtain the therapeutic purpose, as well as avoiding involvement of deeper layers which carries a risk of stenosis, due to healing of muscular layers or even perforation, when muscularis propria is involved.

In the esophageal specimens submitted to argon plasma coagulation, we observed a low incidence of involvement of the muscularis mucosa when the method was applied for short time, being 56% and 67% the frequencies of this involvement for appliances lasting 1 s and 78% to 89% for appliances lasting 3 and 5 s. No significant difference in depth was observed between 50 and 90 W coagulations. Watson *et al*[14] also have not noticed difference in depth related to power setting (from 40 to 99 W), applying the same method in three specimens of esophagus. The involvement of the entire mucosa (including the muscularis mucosa) was also less frequent when argon plasma was applied for shorter time, 52% and 76% for 1 and 3 s, respectively.

Damage to the intermediate mucosa (including the lamina propria) was frequently observed (78% to 89%), independently of the amount of energy used (from 50 to 450 J). As the destruction of the entire mucosa layer is, in theory, the purpose of the endoscopic ablation of Barrett´s metaplasic epithelium, it seems that application of smaller amounts of energy decreases the risk of involvement of the muscularis mucosa, maintaining a good therapeutic result. This is particularly relevant when Barrett involves the whole circumference of the organ, increasing the risk of stenosis. Using argon plasma with 60 W potency for 1 s to destroy Barrett´s Esophagus, Grade *et al*[15] observed intestinal metaplasia below repaired squamous epithelium in 20% of the cases. With this amount of energy they had no complications. Pereira-Lima *et al*[7], Pedrazzani *et al*[6], Schulz *et al*[16] and Ragunath *et al*[17] applied higher amounts of energy of argon plasma, treating patients with Barrett's esophagus (65 to 70 W for 10 s *vs* 90 W for a short interval). Pereira-Lima *et al*[7], Pedrazzani *et al*[6] and Schulz *et al*[16] obtained complete eradication of the metaplastic epithelium, while Ragunath *et al*[17] obtained 65% eradication of the metaplastic epithelium. However, complications as stenosis, pleural infusion, one case of pneumoperitoneum and one case of hemorrhage for ulcer were observed in their series. Injury of the muscularis propria occurred in two coagulation points in our study, when 90 W × 1 s and 50 W × 5 s were used, representing 3.7% of all coagulation points. In Watson´s *et al* study[14], this damage occurred only in 5% of the cases when the time interval was 3 s and Heindorff *et al*[18] described just 1% of perforation when argon plasma was use to permeate esophageal cancer. This shows that despite uncommon, the risk of esophagus perforation with this method exists, even when small amounts of energy are used.

On the stomach wall, argon plasma coagulation resulted in involvement of the intermediate mucosa frequently

Table 1 Involvement of digestive wall layers by argon plasma coagulation in the esophagus

Time	1 s			3 s			5 s		
Power setting	50 W	70 W	90 W	50 W	70 W	90 W	50 W	70 W	90 W
Energy amount	50 J	70 J	90 J	150 J	210 J	270 J	250 J	350 J	450 J
M int	89%	-	78%	89%	-	89%	78%	-	89%
M M	67%	-	56%	89%	-	89%	78%	-	89%
M P	0%	-	11%	0%	-	0%	11%	-	0%

M int: Intermediate mucosa; MM: Muscularis mucosa; MP: Muscularis própria; J: Joule.

Table 2 Involvement of the digestive wall layers by argon plasma coagulation in the stomach

Time	1 s			3 s			5 s		
Power setting	50 W	70 W	90 W	50 W	70 W	90 W	50 W	70 W	90 W
Energy amount	50 J	70 J	90 J	150 J	210 J	270 J	250 J	350 J	450 J
M int	50%[a]	55%[a]	91%	82%	91%	82%	91%	91%	100%
M M	30%[a]	27%[a]	64%	73%	82%	73%	82%	82%	100%
M P	0%	0%	0%	0%	0%	0%	0%	0%	9%

[a]$P < 0.05$ *vs* argon plasma coagulation. M int: Intermediate mucosa; MM: Muscularis mucosa; MP: Muscularis própria; J: Joule.

Table 3 Involvement of digestive wall layers by argon plasma coagulation in the colon

Time	1 s			3 s			5 s		
Power setting	50 W	70 W	90 W	50 W	70 W	90 W	50 W	70 W	90 W
Energy amount	50 J	70 J	90 J	150 J	210 J	270 J	250 J	350 J	450 J
M int	82%	82%	100%	91%	100%	100%	100%	100%	100%
M M	45%[a]	27%[a]	90%	64%[a]	82%	91%	91%	91%	82%
M P	9%	0%	30%	9%	18%	27%	18%	36%	45%

[a]$P < 0.05$ *vs* argon plasma coagulation. M int: Intermediate mucosa; MM: Muscularis mucosa; MP: Muscularis própria; J: Joule.

Table 4 Involvement of the digestive wall layers by bipolar electrocoagulation in the esophagus

Time	1 s		3 s		5 s		10 s	
Power setting	20 W	50 W	20 W	50 W	20 W	50 W	20 W	50 W
Energy amount	20 J	50 J	60 J	150 J	100 J	250 J	200 J	500 J
M int	-	44%	56%	78%	67%	78%	67%	100%
M M	-	22%	33%	44%	22%	67%	44%	78%
M P	-	0%	0%	0%	0%	0%	0%	0%

M int: Intermediate mucosa; MM: Muscularis mucosa; MP: Muscularis própria; J: Joule.

(82% to 100%), when 90 J or more was applied (until 450 J). This energy interval also caused muscularis mucosa injury more often (64% to 100% of cases). In the other hand, the involvement of this layer until 70 J was 27% to 30%. Watson *et al*[14] also noted deeper involvement of the wall when higher power settings for longer intervals were used in three fresh surgical specimens of stomach. However, different stratification of the wall layers did not allow comparisons with our study. Eventual healing retractions of the stomach wall rarely result in clinical manifestation due to the amplitude of its lumen. Indeed, papers describing APC to treat Watermelon Stomach, using 60[19] to 100 W[12] were successful with no complications.

In a similar study, Johanns *et al*[20] described involvement of the muscularis mucosa when 75 W or more, for 5 or 10 s, were applied to the gastric wall. The difference found in our study may be consequent to the small number of specimens of the mentioned study (four). In both papers the involvement of the muscularis propria was rare, being observed only when 90 W × 5 s was applied in ours and 155 W × 10 s was applied in Johann's. These results support the safety of the use of argon plasma coagulation for the treatment of gastric lesions. However as the intermediate mucosa is damaged with the same frequency with 90 J or more, application of higher amounts of energy seems to be unnecessary to treat lesions above the muscularis mucosa. Sebastian´s *et al*[21] results corroborate this theory.

Damage caused by APC to the muscularis mucosa

Table 5 Involvement of the digestive wall layers by bipolar electrocoagulation in the stomach

Time	1 s		3 s		5 s		10 s	
Power setting	20 W	50 W	20 W	50 W	20 W	50 W	20 W	50 W
Energy amount	20 J	50 J	60 J	150 J	100 J	250 J	200 J	500 J
M int	36%	45%	64%	27%	18%	18%	45%	45%
M M	18%	0%	27%	9%	9%	0%	18%	18%
M P	0%	0%	9%	0%	0%	0%	0%	0%

M int: Intermediate mucosa; MM: Muscularis mucosa; MP: Muscularis própria; J: Joule.

Table 6 Involvement of digestive wall layers by bipolar electrocoagulation in the colon

Time	1 s		3 s		5 s		10 s	
Power setting	20 W	50 W	20 W	50 W	20 W	50 W	20 W	50 W
Energy amount	20 J	50 J	60 J	150 J	100 J	250 J	200 J	500 J
M int	64%[a]	60%[a]	55%[a]	100%	91%	100%	82%	90%
M M	9%[a]	30%[a]	27%[a]	55%	55%	82%	64%	60%
M P	0%	0%	0%	0%	0%	0%	9%	10%

[a]$P < 0.05$ *vs* argon plasma coagulation. M int: Intermediate mucosa; MM: Muscularis mucosa; MP: Muscularis própria; J: Joule.

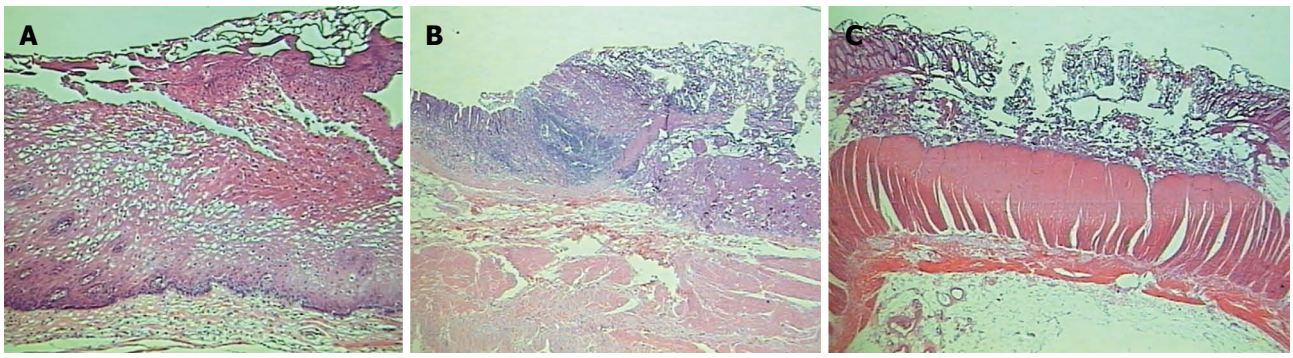

Figure 4 The microscopic aspect of coagulated spots with different depths of coagulation necrosis. A: Microscopic aspect of superficial mucosal involvement. Citoplasmatic acidofilia, cellular picnosis in an esophageal specimen [hematoxylin and eosin (HE), 250 ×]; B: Microscopic aspect of submucosal involvement in a gastric specimen (HE, 250 ×); C: Microscopic aspect of muscularis propria involvement in a colonic specimen (HE, 250 ×).

of the colon was less frequent when up to 70 W × 1 s was applied (27% to 45%). The same interval of energy caused involvement of the intermediate mucosa frequently (82% of the cases). These findings are relevant as stenosis of the colon, similar to the esophagus', usually are symptomatic. This consequence, however, can be minimized using lower amounts of energy, up to 70 J.

Damage of the muscularis propria of the colon occurred even when smaller amounts of energy were used. Although the frequency of this involvement was higher with bigger amounts of energy, reaching 45%, these findings alert to the care to be taken when APC is used in this organ, for the risk of perforation. Indeed, despite the use of a 40 W potency, Wahab *et al*[12] noticed one case of perforation in the cecum. Canard *et al*[22] used APC with 30 to 80 W to treat radiation proctitis and had three severe complications (extensive necrosis, perforation and hemorrhage), all of them when potency was above 45 W.

Vargo[8] reviewed eight papers (151 patients) dealing with the treatment of radiation proctitis with APC in potencies of 40 to 60 W. The incidence of success was high, independently of the power setting. In the other hand, major complications were observed in only three cases, a rectum-vaginal fistulae and two stenosis. These complications could be explained by the use of higher potencies, 50 W and 60 W, respectively. Our results differ from those written by Johanns *et al*[20], who noticed injury of the muscularis propria of the colon, similarly to the esophagus, only when 155 W for 10 s was applied. In their methodology, the authors report fibrosis and cellular picnosis below the coagulation zone. For us, these findings were considered cellular necrosis, justifying the deeper involvement observed here.

The application of bipolar electrocoagulation to esophageal specimens results in more frequent involvement of the intermediate mucosa (67% to 100%) when 100 J or more were used. Damage of the muscularis mucosa were less frequent (up to 44%) when 200 J or less were applied. Between 250 and 500 J this involvement was 67% to 78%. These findings suggest that the interval between 100 and 200 J may be best suited to ablation of the intermediate mucosa, especially in circumferential

lesions with risk of healing retraction. Bipolar electrocoagulation did not resulted in damage of the muscularis propria of the esophagus in this study encouraging its use in clinical practice. Indeed, stenosis and perforation after Barrett´s treatment was significantly less frequently reported with the application of this method.

Kovacs *et al*[23] observed 5% of stenosis with the use of bipolar electro-coagulation on metaplasic epithelium in esophagus. Sampliner *et al*[24] observed only one case of stenosis out of 72 patients treated the same way. Sharma *et al*[25] and Sampliner *et al*[26] had no complications. However success rates were also lower, 81%, 78% and 73%, respectively. Montes *et al*[27] were successful in 100% of their cases by applying bipolar electrical current, with power of 20 W, on Barrett's esophagus; unfortunately the study doesn't specified electrocoagulation time employed. Electrocoagulation with higher power settings and for longer time might optimize the results of this method for the treatment of Barrett´s esophagus, keeping a lower risk for complications when compared to argon plasma. In the other hand, using argon plasma one can cover extensive areas faster than with the use of bipolar coagulation justifying the popularity of the first method. To overcome this limitation, Ganz *et al*[28] published the application of a new electrocoagulation probe with an adjustable balloon that allows contact to the entire circumference of the organ. The device has been used in three patients before surgery for esophageal cancer. Electrocoagulation was performed with 260 to 350 W power settings for 0.8 s (energy density of 10 to 12 J/cm^2). There were no cases of perforation. A histological evaluation of these specimens showed mucosal ablation of 75% to 95% of the treated area in the two cases that the balloon contacted the whole circumference of the organ. The lamina propria was involved in all the three cases, being the muscularis mucosa totally involved in the majority of the coagulated areas. In a preliminary study using a porcine model (n = 12), electrocoagulation of healthy mucosa was performed with 350 W power setting and energy densities varying from 5 to 20 J/cm^2. The application of more than 12 J/cm^2 resulted in involvement of the submucosa and, above 15 J/cm^2; damage of the muscularis propria was seen. There was one case of peri-esophageal effusion when 20 J/cm^2 was used. This result is consistent with our findings, as, despite the ideal interval for these authors be 200 to 280 J, their target was the involvement of the muscularis mucosa. The concept of controlled deliverance of energy to the GI wall culminated with the introduction of radiofrequency ablation for the treatment of Barrett's esophagus. In radiofrequency sessions both the amount of energy and the contact of the balloon-based probe with the mucosal surface are controlled which seem critical to the good results achieved with this technique[29].

In this study, when bipolar electrocoagulation was used, the frequency of involvement of the intermediate mucosa of the stomach was low, up to 45%, except when the combination 20 W × 3 s was used, raising its involvement to 64%. Damage of the muscularis mucosa varied between 0 and 18% in all combinations of power setting and time except with the combination 20 W × 3 s, when it was 27%. This combination was the only one that presented damage to the muscularis propria, in only one coagulated point (9%). There was no correlation between power setting or time of application and involvement of the intermediate mucosa or muscularis mucosa of the stomach. These findings suggest that bipolar electrocoagulation of the stomach surface can be safely applied, even with higher power settings and longer time, as the risk of muscularis mucosa damage is low and muscularis propria very rare.

Although characteristic features of antral vascular ectasia are found in the lamina propria of the mucosa, the variants mentioned above could explain the therapeutic success of bipolar electrocoagulation in the treatment of this condition, like the results observed by Binmoeller *et al*[30] and Jensen *et al*[10].

Morris *et al*[31] studied the effect of this method to the gastric wall of dogs. The animals were maintained alive for the next seven days, when the depth of the wall involvement was analyzed. They observed deeper involvement, using similar combinations of power setting and time than we did. However some considerations can be pointed out. The thickness of the specimens wall was not described, not allowing comparison and, histological analyses took place one week after coagulation. It is not established if this interval is responsible for healing or increasing the thermal lesion.

In the colon, electrocoagulation with smaller amounts of energy, up to 60J (20 W × 3 s), caused injury of the muscularis mucosa less frequently (9% to 30%), while the interval between 100 and 500 J provoked this involvement in 55% to 82%. In the other hand, less frequent muscularis mucosa involvement with less chance of stenosis was obtained with amounts of energy that provoked less damage to the intermediate mucosa (55% to 64% of the cases-up to 60 J and 82% to 100% of involvement-150 to 500 J). When the method was applied for longer interval (10 s), the muscularis propria was involved in 9% to 10% of the coagulated points, similarly to Jensen´s *et al*[32] findings. Although this could be considered a low incidence, this involvement should be pointed out for the risk of perforation. The application for short intervals (up to 5 s), even with 50 W power setting, did not caused muscularis propria damage in any coagulated point, offering better safety for clinical practice.

We would also like to emphasize that in this study as in Jensen´s *et al*[32], cecum specimens, known for presenting a thinner wall, were not used. Application of any thermal method on this colon segment should be performed more cautiously. Radiation lesions are also special situations for being located in ischemic, less resistant tissue.

In this study, electrocoagulation appeared safer than argon plasma also in the colon. Causing a more superficial damage, it seems to be adequate to lesions such as

vascular ectasias. Nevertheless, Jensen *et al*[9] related one case of perforation after treating colonic vascular ectasias.

In conclusion, involvement of the intermediate mucosa of the stomach and of the muscularis mucosa of the stomach and the colon by argon plasma coagulation were more frequent when higher amounts of energy were used (above 90 J). The same tendency was observed in the esophagus samples for the involvement of the muscularis mucosa (above 150 J). In the esophagus and in the colon, injury of the intermediate mucosa caused by this method was frequent, even when small amount of energy was used (50 J). Injury of the muscularis propria was observed in 9% to 45% of the colon samples, depending on the amount of energy used. In the esophagus and in the stomach, the involvement of the muscularis propria was rare.

The use of bipolar electrocoagulation resulted in more frequent involvement of the intermediate mucosa and of the muscularis mucosa of the colon when higher amounts of energy were used (100 J or more). The same tendency was observed in the esophagus samples. In the stomach, the frequency of involvement of the intermediate mucosa and of the muscularis mucosa by the latter method was low, even when more energy was used (until 500 J). The risk of injury of the muscularis propria was low in the stomach and in the colon, not being observed in the esophagus.

Bipolar electrocoagulation seemed to cause more superficial injury to the specimens walls when compared to argon plasma coagulation, however the difference was statistically significant only for stomach specimens.

COMMENTS

Background

The association of diathermy to endoscopy has provided significant advances in endotherapy, which became a valuable alternative to traditional surgery and therapeutic procedure of choice in several conditions (*e.g.*, sphyncterotomy, polypectomy). The best way of applying heat to tissue has not been clearly established for hollow organs so far.

Research frontiers

The best way of applying heat to hollow digestive organs during thermal endoscopic therapy has not been clearly established so far. This study analyzes the histophathological effect of bipolar electrocoagulation and argon plasma coagulation on fresh surgical specimens of the digestive tract.

Innovations and breakthroughs

This study analyzes the histopathological effect of bipolar electrocoagulation and argon plasma coagulation on fresh surgical specimens of the digestive tract. Tissue damage after argon plasma coagulation is deeper than bipolar electrocoagulation. Both of them depend on the amount of energy used.

Applications

The use of argon plasma coagulation is popular in therapeutic endoscopy probably because it is easily available, has low cost, large surfaces of mucosa can be treated in one session and it causes allegedly superficial damage to the GI wall. These findings suggest that lower power settings are probably safer when argon plasma coagulation is employed at the colorectal and esophageal wall.

Terminology

Bipolar coagulation: the passage of electrosurgical current occurs within the accessory. Argon plasma coagulation: the passage of monopolar electrosurgical current occurs through a cloud of argon gas.

Peer review

This study deals with a topic that is very much valued by the endoscopic digestive surgeons, that is the laser argon versus the bipolar coagulator, which one the safer and more effective way of cauterization would be among them two.

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RETROSPECTIVE STUDY

Improved endoscopic retrograde cholangiopancreatography brush increases diagnostic yield of malignant biliary strictures

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Author contributions: All authors contributed equally to this work; Shieh FK, Khara HS, Shellenberger MJ, Johal AS and Diehl DL were involved in the clinical management, procedural performance and tissue acquisition of the cases; Luong-Player A, Liu H and Lin F were involved in the cytopathological analysis and diagnostic assessment of the cases.

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Abstract

AIM: To determine if a new brush design could improve the diagnostic yield of biliary stricture brushings.

METHODS: Retrospective chart review was performed of all endoscopic retrograde cholangiopancreatography procedures with malignant biliary stricture brushing between January 2008 and October 2012. A standard wire-guided cytology brush was used prior to protocol implementation in July 2011, after which, a new 9 French wire-guided cytology brush (Infinity sampling device, US Endoscopy, Mentor, OH) was used for all cases. All specimens were reviewed by blinded pathologists who determined whether the sample was positive or negative for malignancy. Cellular yield was quantified by describing the number of cell clusters seen.

RESULTS: Thirty-two new brush cases were compared to 46 historical controls. Twenty-five of 32 (78%) cases in the new brush group showed abnormal cellular findings consistent with malignancy as compared to 17 of 46 (37%) in the historical control group (P = 0.0003). There was also a significant increase in the average number of cell clusters of all sizes (21.1 *vs* 9.9 clusters, P = 0.0007) in the new brush group compared to historical controls.

CONCLUSION: The use of a new brush design for brush cytology of biliary strictures shows increased diagnostic accuracy, likely due to improved cellular yield, as evidenced by an increase in number of cellular clusters obtained.

Key words: Malignant biliary stricture; Endoscopic retrograde cholangiopancreatography; Brush cytology; Diagnostic yield; Cytopathology

Core tip: The sensitivity of brush cytology for biliary strictures has historically been low (around 30%-60%). Many studies have described efforts to improve cellular yield and diagnostic accuracy with varying success. We describe the development of an improved biliary brush cytology protocol with the use of a new biliary brush design which more than doubled the diagnostic yield of our brush cytology as compared to the historical cases. Cytopathological analysis also showed increased cellular yield, and thus better diagnostic accuracy, with the improved protocol implementation.

Shieh FK, Luong-Player A, Khara HS, Liu H, Lin F, Shellenberger MJ, Johal AS, Diehl DL. Improved endoscopic retrograde cholangiopancreatography brush increases diagnostic yield of malignant biliary strictures. *World J Gastrointest Endosc* 2014; 6(7): 312-317 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i7/312.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i7.312

INTRODUCTION

Brush cytology during endoscopic retrograde cholangiopancreatography (ERCP) remains one of the most common approaches to sample biliary strictures. Cytologic brushing has an excellent safety profile, widespread availability, and is relatively quick and simple to perform[1,2]. However, the reported sensitivity for brush cytology is low, ranging from 30%-60%[3]. Many studies have described efforts to improve cellular yield and diagnostic accuracy. These include disruption of the biliary epithelium by dilating the stricture prior to brushing, two or more brush passes, use of an extra-long cytology brush, immunohistochemistry, cell block method, and mutational analysis, all with varying success[4-15].

Obtaining adequate cellular yield appears to be a key factor in maximizing diagnostic sensitivity and accuracy. In 2011, a new wire-guided cytology brush (Infinity sampling device, US Endoscopy, Mentor, OH) was released for use. This brush has a 9 French sheath, and a combination of stiff and soft bristles designed with the objective of maximizing tissue acquisition. The aim of our study was to see if the use of this new brush would be able to improve the diagnostic sensitivity of ERCP-guided biliary brushing of malignant biliary strictures.

MATERIALS AND METHODS

Retrospective chart review of consecutive ERCPs, performed between January 2008 and October 2012 at our academic center, was conducted. ERCP procedures which involved cytologic brushing of a biliary stricture for suspected malignant biliary obstruction were included in the study. All patients were eventually diagnosed with a malignant biliary obstruction either by endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) or by surgical resection. Our study was approved by the Geisinger Health System Institutional Review Board.

Procedures performed between January 2008 and June 2011 served as historical controls. In this cohort, ERCP cytology brushing was performed with a standard 8 French wire-guided brush (Cytomax, Cook Medical, Bloomington IN; or RX, Boston Scientific, Marlborough MA). Two passes, each with multiple to-and-fro movements across the biliary stricture, were performed. Smears on slides were prepared, and the brush head was then cut off and sent in the cytology transport medium (RPMI).

A standardized protocol was instituted on July 1st, 2011 for ERCP brushing of biliary strictures. All cases were performed with the new 9 French wire-guided cytology brush (Infinity sampling device, US Endoscopy, Mentor, OH) (Figure 1). This brush can be used with a short wire as well as a long wire system. After placement of a biliary guidewire across the stricture, two separate passes, each with multiple to and fro movements, were performed with the brush across the biliary stricture. With the cytologic material collected from the first pass, two touch-prep smears were prepared, one of which was sprayed with fixative (Protocol Cytologic Fixative, Fisher Scientific, Pittsburgh, PA), and the other smear was air-dried. The brush was then agitated in the RPMI cytology fluid to dislodge accumulated cellular material. The brush was subsequently rinsed with water and a second pass was performed with the same brush over the biliary guidewire. The brush was then removed; the brush head was cut off and placed into the same tube of RPMI cytology fluid (Figure 2).

Figure 1 Detail of the 9 French cytology brush (Infinity sampling device, US Endoscopy, Mentor, OH).

Salvage cytology was performed by injecting 5 mL of RPMI cytology fluid through the brush catheter after brushing was completed. The two smear slides and the tube of RPMI containing the brush head and salvage cytology were all submitted to cytology. The smears were stained, and a cell block was made from the tube contents. Smears and cell blocks were reviewed by 2 experienced cytopathologists blinded to the final diagnosis. Cellular yield was meticulously quantified by counting the number and size of cell clusters seen (large clusters > 50 cells, medium clusters 6-49 cells, small clusters 2-5 cells, and single cells). In accordance to current standards in the literature, cytopathological diagnosis of "malignant" or "suspicious" were considered positive, while "atypical" cases were considered negative[9].

RESULTS

Thirty-two new protocol cases and 46 historical controls were analyzed. There were no significant differences in gender (63% *vs* 56% male, respectively, $P = 0.55$), or age (mean 70 *vs* 68 years old, respectively, $P = 0.45$) between the groups. The majority of cases were either pancreatic adenocarcinoma or cholangiocarcinoma as eventually confirmed by EUS-FNA or surgical resection. The degree of the biliary strictures was similar in both

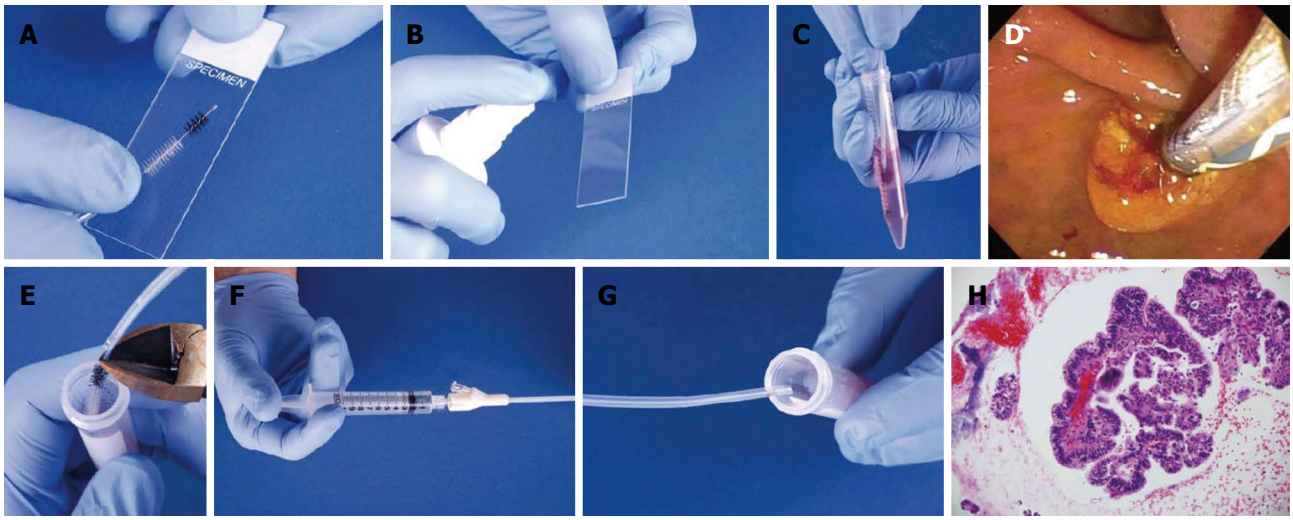

Figure 2 Brushing technique. Two passes performed in the stricture. A, B: The first pass was used to make two smears (A), with one smear sprayed with fixative (B); C: The brush was then agitated in the RPMI cytology fluid to dislodge material into the fluid; D: The brush was rinsed with water. A second pass was performed with the same brush; E: The brush was cut off into the same tube of RPMI; F, G: Contents of catheter were flushed *via* salvage cytology technique; H: The sample was processed as a cell block.

Table 1 Diagnostic yield for the new brush protocol *vs* historical control

	New brush protocol	Historical control	*P* value
Mean age (yr)	70	68	0.45
Gender (males)	63%	56%	0.55
All cases	25/32 (78%)	17/46 (37%)	0.0003
Pancreatic adenocarcinoma	17/23 (74%)	6/20 (30%)	0.005
Cholangiocarcinoma	7/7 (100%)	8/22 (36%)	0.004
Other	1/2 (50%)	3/4 (75%)	0.6
	2 gallbladder cancers	2 gallbladder, 1 colon, 1 unknown	

the groups. The 32 cases in the new protocol cohort consisted of 23 cases of pancreatic adenocarcinoma, 7 cases of cholangiocarcinoma, and 2 gallbladder cancers. Twenty-five of these 32 (78%) cases were diagnosed with malignancy based on biliary brush cytology using the new brush and cytology protocol. The 46 cases in the historical control group consisted of 22 cases of cholangiocarcinoma, 20 cases of pancreatic adenocarcinoma, and 4 others (2 gallbladder cancers, 1 colon cancer, 1 of unknown primary). Seventeen of these 46 (37%) cases were diagnosed with malignancy based on biliary brush cytology using the standard brushes and cytology yield. There was an increased diagnostic yield of brush cytology of these malignant biliary strictures in the new protocol group as compared to the historical controls (P = 0.0003) (Table 1).

There was also a significant increase in the average number of cell clusters of all sizes obtained with the new brush compared to the standard brushes (21.1 *vs* 9.9 clusters, P = 0.0007). This relationship held true when cluster size was broken down into four different categories (large clusters > 50 cells, medium clusters 6-49 cells, small clusters 2-5 cells, and single cells) for all cases. For each of

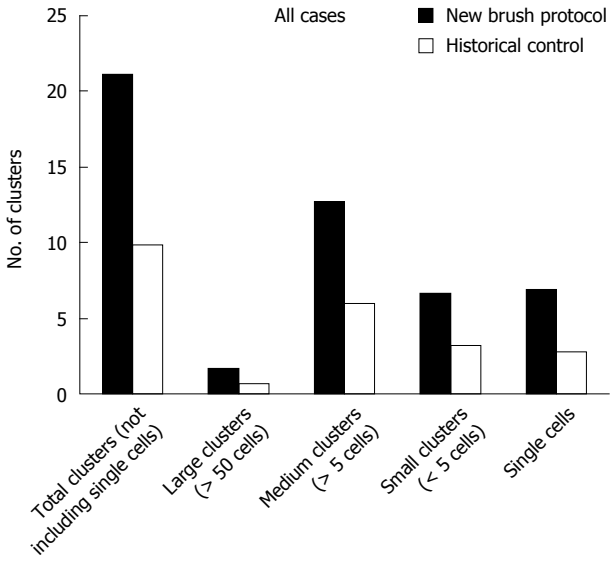

Figure 3 Number of clusters obtained by cytologic brushing for all cases.

the subsets of cluster size, there was a significant increase in the number of clusters in the new brush group compared to the historical control group (P = 0.005, 0.0004, 0.01, 0.009 respectively) (Figure 3).

In the subgroup of patients with pancreatic adenocarcinoma, there was an increase in average total cell clusters of all sizes (20.9 *vs* 6.1, P = 0.001) as well as large, medium, small clusters and single cells (P = 0.0001, 0.0001, 0.0004, and 0.0012, respectively). Diagnostic yield was 74% (17/23) in the new brush group compared to 30% (6/20) in the historical controls, P = 0.005.

Similar results were seen in the subgroup of patients with cholangiocarcinoma, with an increase in average total cell clusters of all sizes (24.6 *vs* 10.8), as well as large, medium, small clusters and single cells (P = 0.04, 0.01, 0.03, and 0.01, respectively). Diagnostic yield was 100%

(7/7) for the new brush group compared to 36% (8/22) in the historical controls, $P = 0.004$.

DISCUSSION

Tissue diagnosis of biliary strictures is of critical importance in treatment planning. This is usually done *via* brush cytology during ERCP, however the diagnostic yield with standard brushings have been low and variable. Changes in technique (predilation, making a second pass, or scraping the stricture with the tip of the cytology brush catheter) can increase yield. Forceps biopsy at the time of ERCP can also be done, with slightly higher diagnostic yield (43%-60%)[3], but can be technically challenging to obtain in some certain cases, especially by less experienced endoscopists. In addition, the diagnostic yield can be low in extrinsic biliary obstruction such as from pancreatic head cancer as compared to cholangiocarcinoma, which typically has an intraductal lesion.

Per-oral cholangioscopy can have sensitivities as high as 78%-89% for the diagnosis of malignancy in indeterminate biliary strictures. However, the utility of this method is limited due several reasons such as scope fragility, requirement of special equipment with high acquisition costs, and requirement of a high level of endoscopic expertise. In addition, "real world" results have not matched those initially obtained by a group of highly skilled biliary endoscopists. Furthermore, tissue sampling is still required for a diagnosis of malignancy which is usually performed through either brush or biopsy methods[6,16,17].

Endoscopic ultrasound allows detailed examination of the common bile duct and pancreatic head, and tissue sampling can be performed *via* EUS-FNA with diagnostic yield as high as 89%[12,18-21]. However, many patients who undergo EUS-FNA for the diagnosis of ductal malignancy will have already undergone ERCP with brushing, and there are costs associated with the second procedure. If EUS-FNA is done in cases of cholangiocarcinoma, there is the potential for tumor seeding. In fact, the Mayo Clinic protocol for liver transplantation in cholangiocarcinoma considers FNA to be a contraindication to liver transplantation[12,22,23]. Probe-based confocal laser endomicroscopy is a newer technology which can offer real-time histologic evaluation of indeterminate biliary strictures during ERCP with overall diagnostic accuracy of over 80%, but it is not widely available, and further studies need to be performed prior to more generalized use[24-28].

A potentially unrecognized source of variability in sampling is how specimens are handled after they are obtained. Some endoscopists always make a smear, and some never do. Some cytology departments always make a cell block and some do this only on request. There is evidence that creation of a cell block can increase the cellular yield and ability to interpret architecture, thereby increasing the sensitivity of cytodiagnosis compared to conventional smears[15]. Multiple studies have consistently shown that cell block along with smear cytology can markedly improve both the sensitivity and specificity of cytologic specimens in the diagnosis of malignancies, especially when the diagnosis from smear alone is non-diagnostic, and that it is cost-effective[29-34]. The increased quantitative cytology yield is also useful if more specialized tests are required on the tissue. For example, detection of aneuploidy *via* digital image analysis (DIA) or fluorescence in situ hybridization (FISH) may be useful in increasing the diagnostic yield in certain difficult indeterminate biliary strictures[35].

Several aspects of the new brush design are likely to have contributed to improved results. The new brush incorporates an increased brush diameter and length, as well as a new bristle design. Stiffer bristles are present on the proximal and distal ends of the brush, which may dislodge more underlying tissue due to a more abrasive effect. Softer bristles in the middle of the brush are then able to capture the abraded material. Some authors recommend removing the brush and catheter as a unit, to prevent loss of cellular material[5]. The new brush also has a slightly larger catheter (9 French compared to 8 French) which decreases the "squeegee effect" of causing tissue loss from the bristles when the brush is retracted. This slightly bigger catheter size did not cause any technical difficulties in advancing the brush over the biliary wire to the desired location as compared to the 8 French brushes. The ability to collect cells for so-called "salvage cytology" from the brush sheath may also contribute to the increase in the amount of tissue collected[36,37]. It is logical that more tissue disruption prior by brushing can improve cellular yield; which is supported by studies demonstrating that two consecutive brushings improved cancer detection rate from 33% to 44%[7], and three consecutive brushings increased the rate from 40% to 60%[38]. In the new brush protocol, we uniformly performed two passes, which may also have contributed to the better diagnostic yield. One limitation of our study is that it is a retrospective review, and the new brush was used in conjunction with a standardized brushing and specimen processing protocol, which may potentially affect the outcomes of the results. However, other than the brush design itself, the tissue acquisition and processing technique was similar in both groups.

With the use of a newly designed ERCP cytology brush, we were able to more than double the diagnostic yield of our brush cytology. Proper specimen processing with the production of smears as well as cell-blocks further increases the cytologist's ability to make a firm diagnosis on the obtained tissue. When it comes to the pathologist's point of view, "tissue is the issue" and increased tissue yields improves the pathologist's ability to make a diagnosis in cases of potentially malignant biliary stricture.

ACKNOWLEDGMENTS

Data from this study was presented in May 2013 as a

poster presentation at Digestive Disease Week 2013 in Orlando, FL, United States.

COMMENTS

Background

The sensitivity of brush cytology for biliary strictures during endoscopic retrograde cholangiopancreatography has historically been low (around 30%-60%) despite various technical variations.

Research frontiers

There is a great need to improve the diagnostic yield of biliary brushings, which is most common and widely used modality for evaluation of biliary strictures.

Innovations and breakthroughs

Many studies have described efforts to improve cellular yield and diagnostic accuracy. These include disruption of the biliary epithelium by dilating the stricture prior to brushing, two or more brush passes, use of an extra-long cytology brush, forceps biopsy method, per-oral cholangioscopy, endoscopic ultrasound-guided fine needle aspiration, probe-based confocal laser endomicroscopy, immunohistochemistry, cell block method, fluorescence *in situ* hybridization and mutational analysis, all with varying success.

Applications

The goal was to determine if by simply using a new brush design and implementing a standardized cytology processing protocol would improve the diagnostic yield of biliary stricture brushings as compared to historical controls.

Peer review

This is a well-written manuscript dealing with an interesting topic. The methodology is straight-forward and the conclusions drawn are in concern with the logics and results of the study.

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RETROSPECTIVE STUDY

Conservative approach in Peutz-Jeghers syndrome: Single-balloon enteroscopy and small bowel polypectomy

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Abstract

AIM: To assess the usefulness of the balloon assisted enteroscopy in preventing surgical intervention in patients with Peutz-Jeghers syndrome (PJS) having a small bowel large polyps.

METHODS: Seven consecutive asymptomatic pts (age 15-38 years) with PJS have been collected; six underwent polypectomy using single balloon enteroscopy (Olympus SIF Q180) with antegrade approach using push and pull technique. SBE system consists of the SIF-Q180 enteroscope, an overtube balloon control unit (OBCU Olympus Balloon Control Unit) and a disposable silicone splinting tube with balloon (ST-SB1). All procedures were performed under general anesthesia. Previously all pts received wireless capsule endoscopy (WCE). Prophylactic polypectomy was reserved mainly in pts who had polyps > 15 mm in diameter. The balloon is inflated and deflated by a balloon control unit with a safety pressure setting range from -6.0 kPa to +5.4 kPa. Informed consent has been obtained from pts or parents for each procedure.

RESULTS: Six pts underwent polypectomy of small bowel polyps; in 5 pts a large polyp > 15 mm (range 20-50 mm in diameter) was resected; in 1 patient with WCE negative, SBE was performed for previous surgical resection of gastrointestinal stromal tumors. In 2 pts endoscopic clips were placed due to a polypectomy. No surgical complication have been reported. SBE with resection of small bowel large polyps in PJS pts was useful to avoid gastrointestinal bleeding and emergency laparotomy due to intestinal intussusceptions. No gastrointestinal tumors were found in subsequent enteroscopic surveillance in all seven pts. In order surveillance, all pts received WCE, upper endoscopy, ileocolonoscopy every 2 years. No pts had extraintestinal malignant lesions. SBE was performed when WCE was positive for significant polyps (> 15 mm).

CONCLUSION: The effective of prophylactic polypectomy of small bowel large polyps (> 15 mm) could be the first line treatment for conservative approach in management of PJS patients.

Key words: Peutz-Jeghers syndrome; Balloon assisted enteroscopy; Polypectomy

Core tip: Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by mucocutaneus pigmentation and multiple polyps in small bowel. Most of pts need surgical intervention for intussusceptions and gastrointestinal bleeding; the surgical risk is up to 50% in pts having a large polyps > 15 mm or rapidly growing. Enteroscopy balloon assisted with resection of

small bowel large polyps is useful to avoid emergency laparotomy after performing wireless capsule endoscopy. The effective of prophylactic polypectomy of small bowel large polyps could be the first line treatment for conservative approach in management of PJS patients.

Torroni F, Romeo E, Rea F, De Angelis P, Foschia F, Faraci S, Federici di Abriola G, Contini AC, Caldaro T, Dall'Oglio L. Conservative approach in Peutz-Jeghers syndrome: Single-balloon enteroscopy and small bowel polypectomy. *World J Gastrointest Endosc* 2014; 6(7): 318-323 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i7/318.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i7.318

INTRODUCTION

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant hereditary disease due to mutation in serine/threonine kinase 11 tumour suppressor gene (STK 11 or LKB1), located on chromosome 19p13.3. The estimated incidence of PJS ranges between 1 in 50000 and 1 in 200000 live births[1]; it is characterized by mucocutaneous melanin pigmentation and hamartomatous polyps in the gastrointestinal tract[2]. These polyps are predominant in the small intestine (prevalence 64%), usually in the jejunum, followed by stomach and colon. The size of polyps requiring endoscopy resection for the high risk of intussusceptions, bleeding, obstruction and malignant transformation, has been considered > 15-20 mm in patients with polyposis[3]. However, the most frequent complication of PJS which occurred during the first decade of life, is intussusception that often needs multiple laparotomies with intestinal enterotomy that increase the risk for short-gut syndrome[4,5]. In the last few years, different diagnostic techniques have been developed for the assessment and therapeutic approach of small bowel polyps, such as small bowel follow-through, wireless capsule endoscopy (WCE), enteroclysis, magnetic resonance and balloon assisted enteroscopy (BAE). PJS is one of the most significant disease that benefit from WCE and BAE for management of this intestinal pathology. The diagnostic yield of WCE has been studied in PJS; usually it is safe, well tolerated and important for the detection of small bowel polyps smaller than 5 mm. When large polyps (> 15 mm) are detected, endoscopic intervention may be required to remove them. BAE is successfully used for surveillance and treatment in patients with PJS[6]. Since 2009, in our Istitution we are using single balloon enteroscopy (SBE) in pts with PJS for radical polypectomy that could provide a means of prophylactic polypectomy to prevent complications and avoid the need for laparotomy.

MATERIALS AND METHODS

Since 2009, we collected seven consecutive asymptomatic PJS pts (4 male, 3 female; age 15-38 years, mean age 22.2 years; weight 50-72 kg) underwent SBE (Olympus SIF Q180 enteroscope Olympus Optical Co., Tokyo, Japan) with anterograde approach and push and pull technique. Clinical and endoscopic characteristics of pts are summarized in Table 1.

Before SBE procedure, all pts received upper endoscopy, ileo-colonoscopy and WCE (GIVEN Imaging Ltd., Yoqneam, Israel) to detect polyps' location and size. WCE allows only an approximate estimation of the size of polyps based on previous experience, however, we estimated polyps size according to small bowel lumen size. The location of small-bowel polyps was estimated by analyzing the WCE transit time between pylorus passage and ileocecal valve. Prophylactic polypectomy was reserved mainly in patients who had polyps > 15 mm in diameter. SBE system consists of the SIF-Q180 enteroscope, an overtube balloon control unit (OBCU Olympus Balloon Control Unit) and a disposable silicone splinting tube with balloon (ST-SB1). The balloon is inflated and deflated by a balloon control unit with a safety pressure setting range from -6.0 kPa to +5.4 kPa. All procedures were performed under general anesthesia. Informed consent has been obtained from pts or parents for each procedure. Peroral insertion required the patient fast for 12 h. Perrectal insertion was not necessary because location of large polyps was predominantly in jejunum and proximal ileum. We performed polypectomy with a polypectomy snare and removed the excised polyp for histological evaluation. Polypectomy was carried out with ENDO CUT Q, a monopolar high frequency electrosurgical technique, based on cutting and coagulation cycles. All pts received intraoperative antibiotic prophylaxis. Fluoroscopic guidance was used when necessary to verify the correct looping and the withdrawal maneuvers of the endoscope. No hemoclips on the polyp pedicle prior to the polypectomy was placed to avoid post polypectomy bleeding. WCE and BAE were performed approximately every 2 years for surveillance and treatment of polyps. All pts underwent abdominal and testicular ultrasonography to exclude malignant extraintestinal complications. Ethical approval for this study was obtained from our ethics board.

RESULTS

Six pts underwent polypectomy of small bowel polyps; in these pts polyps were located in jejunum and proximal ileum according to WCE investigation previously performed (Figure 1). Five pts underwent to extensive polypectomy of small bowel large polyps > 15 mm in diameter (20 mm until 50 mm) (Figure 2); from three to five small bowel large polyps were removed in 5 pts. In one case WCE was normal; this patient underwent SBE for previous surgical resection for gastrointestinal stromal tumors (GIST); SBE was normal. Histological evaluation showed hamartoma tissue in all polyps retrieved. No bleeding or surgical complications have been reported; no complications due to SBE occurred after procedures. In 2 pts endoscopic clips have been placed on a large tearing of intestinal mucosa due to polypectomy procedure (Figure

Table 1 Patient characteristics

Patients	Sex	Age (yr)	Previous surgery	WCE	SBE	No. of polyps removed in small bowel	Size of polyps (mm)	Histology
1	M	35	Intussusceptions	Jejunal large polyps	Proximal jejunal polyps	5	40	Hamartomatous polyps
2	M	34	Intussusceptions	Jejunal polyps	Proximal jejunal polyps	3	10	Hamartomatous polyps
3	F	16	Intussusceptions	Jejunal large polyps	Distal jejunal polyps	4	20	Hamartomatous polyps
4	F	21	Intussusceptions Laparotomy for perforation following colonic polyp	Jejunal large polyps	Proximal jejunal polyps	5	50	Hamartomatous polyps
5	M	31	Intussusceptions Lapatotomy for GIST	Normal	Normal (Biopsies)	-	-	Normal
6	M	17	Intussusceptions	Jejunal large polyps	Proximal jejunal polyps	4	40	Hamartomatous polyps
7	F	16	Intussusceptions	Jejunal large polyps	Proximal jejunal polyps	3	50	Hamartomatous polyps

GIST: Gastrointestinal stromal tumors; WCE: Wireless capsule endoscopy; SBE: Single balloon enteroscopy.

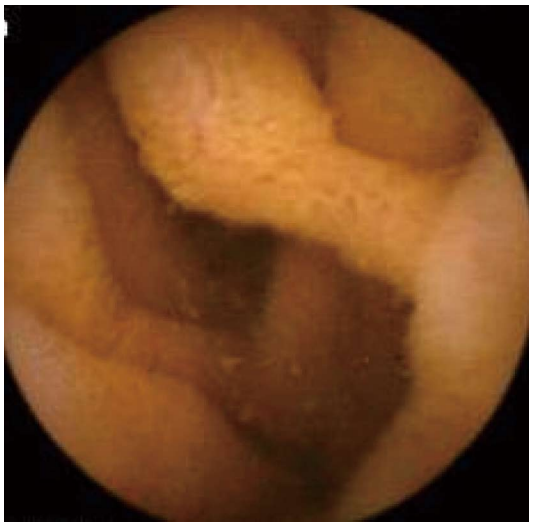

Figure 1 Wireless capsule endoscopy: Jejunal polyp.

3). Three of seven pts had multiple gastric micro polyps; no polypectomy was done. Four pts had multiple sessile colonic polyps, one of them with large multiple polyps underwent polypectomy. The mean procedure time was 72 min (range 60-120 min). Mean time of discharge of pts was 2 d. All pts had previous surgical resections of small bowel for polyps due to obstruction or intussusceptions. No gastrointestinal tumors were found in subsequent enteroscopic surveillance in all seven pts. All pts received WCE, upper endoscopy, ileocolonoscopy every 2 years. No pts had extraintestinal malignant lesions. SBE was performed when WCE was positive for significant polyps (> 15 mm).

DISCUSSION

PJS is characterized by hamartomatous polyps of small bowel predominantly located in the proximal jejunum. The majority of patients with PJS had a history of small bowel surgery. The risk of intussusception and intestinal obstruction before the age of 20 years is up to 50% in particular in patients having a large polyps > 15 mm or rapidly growing[6-8]. In the last few decades, several advanced endoscopic technique have been developed to allow a visualization of small bowel and therapeutic approach without surgery. Before the introduction of BAE, small bowel polyps were removed only by intraoperative endoscopy or surgical resection; now with BAE[9] it is possible to remove proximal end distal small bowel polyps endoscopically, preventing abdominal surgery. WCE and SBE play an important role in surveillance of patients affected by PJS. WCE is safe, well tolerated and permits to detect size, aspect and location of polyps on the entire length of the digestive tube[10,11]. In our series, all patients received upper endoscopy, ileocolonoscopy and WCE to detect polyps' location and size before SBE procedure. WCE allows only an approximate estimation of the size of polyps; therefore, based on previous experience, we estimated polyps size according to small bowel lumen size. Katsinelos *et al*[12] estimated size polyps as small or large, using an open pylorus orifice (diameter 10 mm) as a reference for polyp size estimation. BAE offers diagnostic and therapeutic options for small bowel surveillance in PJS patients[9]; it is a safe procedure also in patients with previously abdominal surgery and in children[13,14]. When significant polyps are detected (> 15 mm), BAE should be the preferred method for prophylactic polypectomy[15]; Sakamoto *et al*[3] reported no intussusceptions developed in all pts underwent small bowel polypectomy. In our experience, endoscopic resection of small bowel large polyps was important to reduce the risk of acute intestinal intussusceptions or obstruction in all seven pts; no patients underwent small bowel resection during the surveillance. Small bowel surveillance is recommended every 2-3 years for pts with PJS from the age of 8-10 years by WCE[16] and endoscopy; removal of significant small bowel polyps reduces emergency surgery[15-17]. Our surveillance program provide a screen-

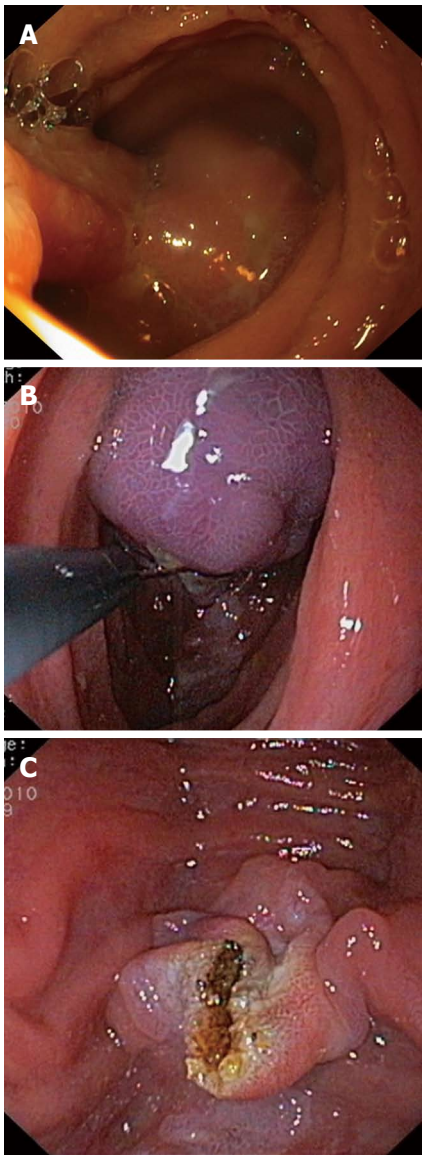

Figure 2 Extensive polypectomy of small bowel large polyps > 15 mm of diameter. A: Large jejunal polyp; B: Polypectomy: polyp captured with snare; C: Polyps pedicle post-polypectomy.

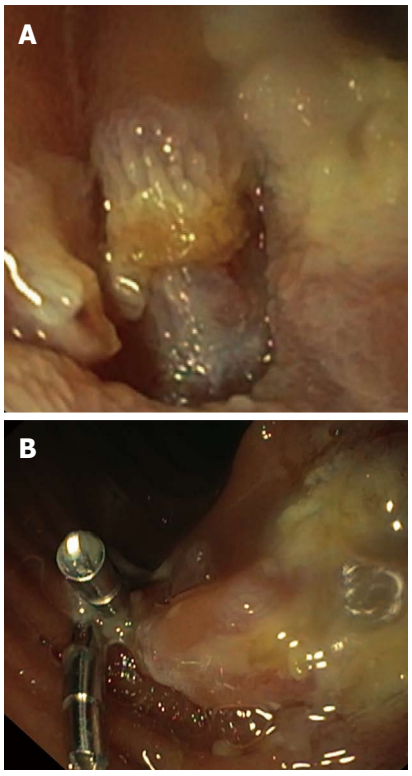

Figure 3 Endoscopic photograph. A: Tearing of intestinal mucosa post-polypectomy; B: Hemoclip placement.

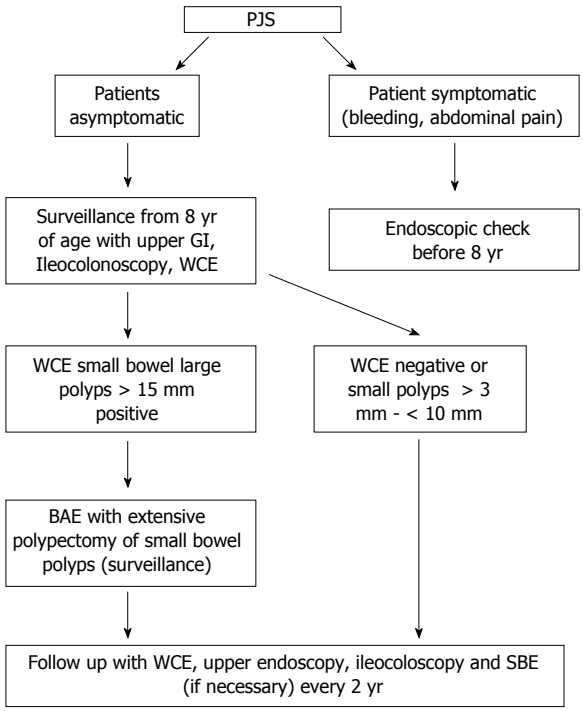

Figure 4 Surveillance algorithm. PJS: Peutz-Jeghers syndrome; WCE: Wireless capsule endoscopy; BAE: Balloon assisted enteroscopy; SBE: Single balloon enteroscopy. GI: Gastrointestinal.

ing from 8 years or earlier if symptomatic (bleeding, abdominal pain) with upper endoscopy, colonoscopy, WCE and SBE according to WCE polyps detection. We suggest elective polypectomy with SBE when significant small bowel polyps are detected (> 15 mm) and laparotomy when polypectomy is not possible (size of polyps > 5 cm or high risk of complications). Follow up with WCE, upper endoscopy and SBE, if necessary, is recommended every 2 years in asymptomatic pts (Figure 4). Cancer predisposition in patient with PJS is known; the risk involves the small bowel, stomach, colon, pancreas and extraintestinal organs as Sertoli cells, breast and ovary. Intestinal polyps can transform in cancer; the risk is related to their dimension, even if malignant transformation is found occasionally in PJS polyps; however transformation sequence hamartoma-adenoma-carcinoma has been described[18-20]. It seems that there is no risk of tumor for the polyps smaller than one centimeter in patients with PJS[9]. No gastrointestinal tumor was found in our patients series during follow-up. In the

past, one of our patients underwent surgical small bowel resection for gastrointestinal tumor, classified as a GIST at surgical specimen examination. Endoscopic polypectomy is a standardized technique and is not without risk. The hemoclip placement can be requested immediately after polyp resection[21,22]; in one of our cases hemoclip was used to avoid a post polypectomy complication due to a large tearing of small bowel mucosa. No bleeding and surgical complications have been reported after SBE procedure in our patients.

In a conclusion, PJS is a pathological condition that require a regular follow-up and screening during the life[23,24]; WCE and SBE procedures with resection of small bowel significant polyps are useful in asymptomatic patients to avoid severe gastrointestinal bleeding and emergency laparotomy due to intussusceptions[25]. About this, we reported our surveillance program that could be useful to follow-up patients affected by PJS. The effective of prophylactic polypectomy of small bowel large polyps could be the first line treatment for conservative approach in management of PJS patients.

COMMENTS

Background

The major problems in the management of Peutz-Jeghers syndrome (PJS) are a large small-bowel polyps, which can cause intussusception and bleeding. The most of pediatric patients with PJS undergo a laparotomy for an episode of intestinal obstruction before they reached 18 years of age and a second laparotomy within 5 years. Balloon assisted enteroscopy (BAE) and wireless capsule endoscopy (WCE) play an important role for diagnostic, care and screening of a large small bowel polyps. Cancer predisposition in patient with PJS is known; transformation sequence hamartoma-adenoma-carcinoma has been described. Surveillance protocols in PJS have two main purposes: one is to detect sizeable gastroenterological polyps which could cause intussusception/obstruction or bleeding/anaemia, second is the detection of cancer at an early stage.

Research frontiers

The need for endoscopic access to improve diagnosis and treatment of small bowel disease has led to the development of novel technologies one of which is non-invasive, the video capsule, and a type of invasive technique, the device-assisted enteroscopy. Before the introduction of BAE, small bowel polyps were removed only by intraoperative endoscopy or surgical resection; now with BAE it is possible to remove proximal end distal small bowel polyps endoscopically, preventing abdominal surgery. Also WCE is a useful examination for the supervision of small intestinal polyposis and PJS; BAE and WCE are complementary investigations in the assessment of small bowel diseases that led to a radical change in their management.

Innovations and breakthroughs

The authors described a method to avoid the risk of surgery using a conservative approach proposing a surveillance algorithm in the management of patient with PJS. Surveillance program provides a screening from 8 years in asymptomatic pts or earlier (before 8 years) if symptomatic with upper endoscopy, colonoscopy, WCE and SBE according to WCE polyps detection. We suggest elective polypectomy with SBE when significant small bowel polyps are detected (> 15 mm) and laparotomy when polypectomy is not possible (size of polyps > 5 cm or high risk of complications).

Applications

The manuscript suggests that it is possible to manage PJS patients using a conservative approach with single balloon enteroscopy (SBE) and capsule endoscopy investigations. This technique should be used in dedicated pediatric endoscopy centers.

Terminology

BAE is a procedure which can allow advancement of long endoscope (200 cm) into the small bowel for diagnostic and therapeutic purposes. BAE uses one or two balloon systems. The system using two balloons is called double balloon enteroscopy and the system using a single balloon is called SBE.The procedure can be performed via the upper gastrointestinal (GI) tract (antegrade) or through the lower GI tract (retrograde).

Peer review

This study describes a safe and useful technique for treatment of small bowel large polyps in patients with polyposis syndrome. The application of the balloon assisted enteroscopy may avoid surgical intervention in patients with Peutz-Jeghers syndrome. It is well written.

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CASE REPORT

Endoscopic and imaging appearance after injection of an ano-rectal bulking agent

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Author contributions: Papafragkaki H and Changela K contributed equally to this work, contributed to conception and design, drafting manuscript part; Bhatia T, Ona MA, Malieckal A and Paleti V contributed to revision of manuscript, acquisition and editing images; Fuksbrumer MS and Anand S contributed to critical revision of the manuscript for important intellectual content.
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Abstract

The use of hyaluronic acid and dextranomer (Solesta, Salix) injection in the anal canal is an emerging modality in the treatment of fecal incontinence. However, little is known regarding the endoscopic and radiological appearance following injection of this ano-rectal bulking agent. We report computed tomography and endoscopic findings after hyaluronic acid/dextranomer injection in the ano-rectal area.

Key words: Fecal incontinence; Ano-rectal bulking agent; Hyaluronic acid; Dextranomer

Core tip: The use of hyaluronic acid and dextranomer (Solesta, Salix) injection in the ano-rectum is an emerging modality in the treatment of fecal incontinence. Our case discusses the endoscopic and radiological findings after injection of this bulking agent in the ano-rectal area.

Papafragkakis H, Changela K, Bhatia T, Ona MA, Malieckal A, Paleti V, Fuksbrumer MS, Anand S. Endoscopic and imaging appearance after injection of an ano-rectal bulking agent. *World J Gastrointest Endosc* 2014; 6(7): 324-327 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i7/324.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i7.324

INTRODUCTION

Fecal incontinence (FI) is defined as the involuntary loss of liquid or solid stool for more than one month. The prevalence of FI ranges between 1.6% and 15%[1,2]. FI is an underdiagnosed condition that may cause psychosocial stigma and poses a clinical challenge to treat. The use of hyaluronic acid and dextranomer (Solesta, Salix) injection in the anal canal is an emerging modality in the treatment of fecal incontinence. However, little is known regarding the endoscopic and radiological appearance following injection of this ano-rectal bulking agent.

CASE REPORT

An 89-years-old woman underwent injection of hyaluronic acid/dextranomer in the anal canal for fecal incontinence under endoscopic guidance (Figure 1). Two days later, the patient had computed tomography (CT) scan of the abdomen and pelvis, which showed mural rectal thickening with multiple round hypodense foci within the rectal wall (Figure 2). Mucinous mural adenocarcinoma and abscess were among the radiological differential diagnosis.

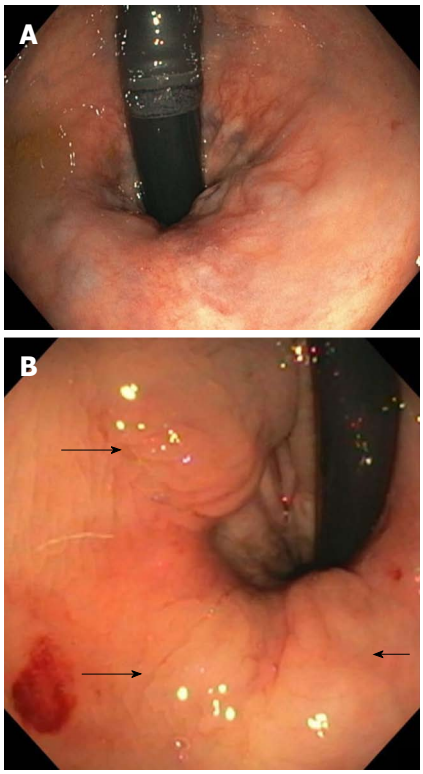

Figure 1 Endoscopic view. A: Endoscopic view of anal canal before hyaluronic acid/dextranomer (Solesta, Salix) injection; B: Endoscopic view of post-hyaluronic acid dextranomer (Solesta, Salix) injection showing the submucosal bulking property of the agent (black arrows).

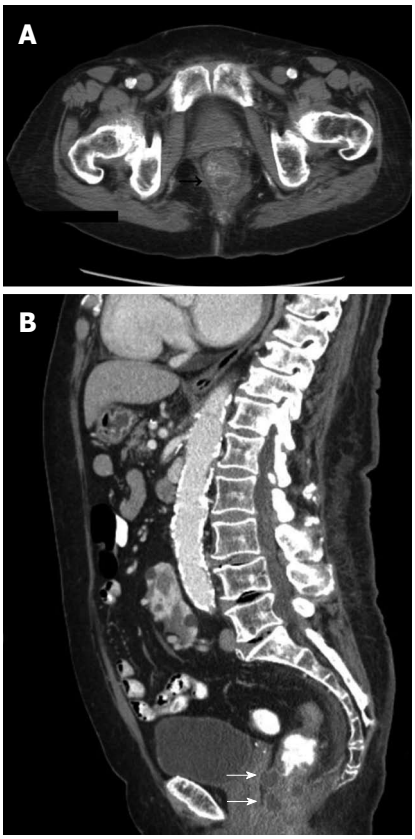

Figure 2 Computed tomography scan. A: Computed tomography scan axial view showing mural thickening with multiple rounded hypodense foci within the posterior rectal wall; B: Computed tomography scan sagittal view showing multiple rounded foci within the anterior and posterior rectal wall (white arrows).

DISCUSSION

We report a case of CT and endoscopic findings after hyaluronic acid/dextranomer injection in the ano-rectal area.

Current treatment options for FI include conservative measures, medications and surgery. Conservative approaches include pelvic floor muscle training, diet modifications, use of pads or plugs and biofeedback[3-5]. Biofeedback, assisted by a therapist and using electrodes placed on the abdomen and in the rectum, can help patients gain control of the pelvic musculature and improve FI symptoms. A study by Lacima *et al*[6] demonstrated that the majority of patients managed with biofeedback achieved 75% reduction in incontinence episodes or fully recovered compared to controls.

Medical management of FI commonly begins with antidiarrheals, such as loperamide, although their use is often limited by the development of constipation[7]. Amitriptyline, a tricyclic antidepressant, is also used for the management of FI, however, with modest efficacy[8]. Clonidine, a centrally acting α_2 adrenergic agonist, has been demonstrated to reduce symptoms and increase incontinence-free days in women with predominantly urge-related fecal incontinence[9].

Invasive interventions are currently the last resort for the management of FI. They include sacral nerve stimulation, radiofrequency treatment and surgery. The exact mechanism of action of sacral nerve stimulators is not fully understood, but it is thought to be related to improved ano-rectal angulation and amplification of anal closing pressures[10]. Radiofrequency treatment causes a topical burn with subsequent remodeling and tightening of the ano-rectal muscles and has shown conflicting results in the management of FI[11]. More studies are needed to establish the efficacy and application of this treatment modality. Surgery remains the last resort for refractory FI. The long term results after sphincter repair are modest[12-14]. In patients with internal rectal prolapse, anterior rectopexy may be promising as an alternative surgical approach[15]. The use of an artificial anal sphincter or a magnetic anal sphincter are other novel surgical approaches, but more studies are needed to establish their use[16].

The use of hyaluronic acid/dextranomer (Solesta, Salix), a non-allergenic, biocompatible bulking agent, which causes a tissue-like formation in the anal canal can provide an alternative to surgical treatment when conservative management has failed. Hyaluronic acid/dextranomer (Solesta, Salix) applied through transanal submucosal injection provides support for the ingrowth of fibroblasts and collagen[17]. The 12-mo efficacy and safety of this ano-rectal bulking agent has been demonstrated in trials[10,18]. A recent study by La Torre *et al*[19] demonstrated the efficacy and durability of a hyaluronic acid/dextrano-

mer agent 24 mo after use. Almost 63% of the patients demonstrated good response and had more than 50% reduction of incontinence episodes 24 mo after injection.

Hyaluronic acid/dextranomer application is increasing as more physicians are aware of its efficacy in the management of FI. However, little is known regarding the radiological and endoscopic appearance after its use. As demonstrated in our report, the CT findings may show mural rectal thickening with hypodense foci within the ano-rectal wall, which may mimic abscess or tumor. There have been anecdotal reports of surgical removal of ano-rectal bulking agent implants due to confusion about its appearance. These changes are likely permanent and therefore, it is important for gastroenterologists, surgeons and radiologists to be cognizant of the endoscopic and radiological appearance of the ano-rectum after hyaluronic acid/dextranomer injection and inquire about previous bulking agent injection in that area.

COMMENTS

Case characteristics

An 89-years-old woman underwent injection of hyaluronic acid/dextranomer in the anal canal for fecal incontinence under endoscopic guidance.

Clinical diagnosis

Fecal incontinence.

Differential diagnosis

Mucinous mural adenocarcinoma, abscess.

Imaging diagnosis

Computed tomography (CT) scan axial view showed mural thickening with multiple rounded hypodense foci within the posterior rectal wall. CT scan sagittal view showed multiple rounded foci within the anterior and posterior rectal wall. Endoscopic view of post-hyaluronic acid/dextranomer (Solesta, Salix) injection showed the submucosal bulking property of the agent.

Treatment

Submucosal injection of hyaluronic acid/dextranomer (Solesta, Salix) into the ano-rectum.

Related reports

Little is known regarding the endoscopic and radiological appearance following injection of this ano-rectal bulking agent.

Term explanation

Hyaluronic acid/dextranomer (Solesta, Salix) is a non-allergenic, biocompatible bulking agent, which causes a tissue-like formation in the anal canal that can provide an alternative to surgical treatment when conservative management for fecal incontinence has failed.

Experiences and lessons

As demonstrated in our report, computed tomography findings may show mural rectal thickening with hypodense foci within the ano-rectal wall after injection of the ano-rectal bulking agent, which may mimic the appearance of an abscess or tumor; thus, it is important for clinicians to be cognizant of the endoscopic and radiological appearance of the ano-rectum after hyaluronic acid/dextranomer injection, to inquire about previous bulking agent injection in the anal canal, and to include this in the differential diagnosis.

Peer review

These authors showed the interesting finding of computed tomography and endoscopic findings after hyaluronic acid/dextranomer injection in the ano-rectal area. As it is demonstrated in their report, the computed tomography findings may show mural rectal thickening with hypodense foci within the ano-rectal wall, which may mimic abscess or tumor.

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CASE REPORT

Intraductal papillary mucinous neoplasm of the bile duct with gastric and duodenal fistulas

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Abstract

Intraductal papillary mucinous neoplasm (IPMN) of the bile duct is still rare and not yet understood despite of its increased incidence and similar clinicopathologic characteristics compared with IPMN of the pancreas. The fistula formation into other organs can occur in IPMN, especially the pancreatic type. To our knowledge, only two cases of IPMN of the bile duct with a choledochoduodenal fistula were reported and we have recently experienced a case of IPMN of the bile duct penetrating into two neighboring organs of the stomach and duodenum presenting with abdominal pain and jaundice. Endoscopy showed thick mucin extruding from two openings of the fistulas. Endoscopic suction of thick mucin using direct peroral cholangioscopy with ultra-slim endoscope through choledochoduodenal fistula was very difficult and ineffective because of very thick mucin and next endoscopic suction through the stent after prior insertion of biliary metal stent into choledochogastric fistula also failed. Pathologic specimen obtained from the proximal portion of the choledochogastric fistula near left intrahepatic bile duct through the metal stent showed a low grade adenoma. The patient declined the surgical treatment due to her old age and her abdominal pain with jaundice was improved after percutaneous transhepatic biliary drainage with the irrigation of N-acetylcysteine three times daily for 10 d.

Key words: Intraductal papillary mucinous neoplasm; Bile duct; Fistula; Acetylcysteine

Core tip: An intraductal papillary mucinous neoplasm of the bile duct with combined fistula formation into the stomach and the duodenum initially presented with jaundice and abdominal pain was introduced and after failed attempts of endoscopic suction of thick mucin through the two fistulas to resolve the jaundice, the patient's symptom was successfully resolved after the irrigations of N-acetylcysteine three times daily *via* after percutaneous transhepatic biliary drainage tube for 10 d.

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INTRODUCTION

Intraductal papillary mucinous neoplasm (IPMN) of the bile duct has been suggested to be the biliary counterpart of IPMN of the pancreas after wide acceptance of the nomenclature by the World Health Organization[1]. It represents a disease spectrum from benign to malignant and affected bile ducts exhibit marked dilatation because of mucin hypersecretion. Jaundice with cholangitis is sometimes complicated by the presence of intraductal tumor with tenacious mucoid impaction[2,3]. The fistula from penetration into other neighboring organs can be caused by high pressure due to mucin-filling of bile ducts and inflammatory stimulation[4]. IPMN of the bile duct with fistula formation into surrounding organs was relatively rare presentation compared with its pancreatic counter-

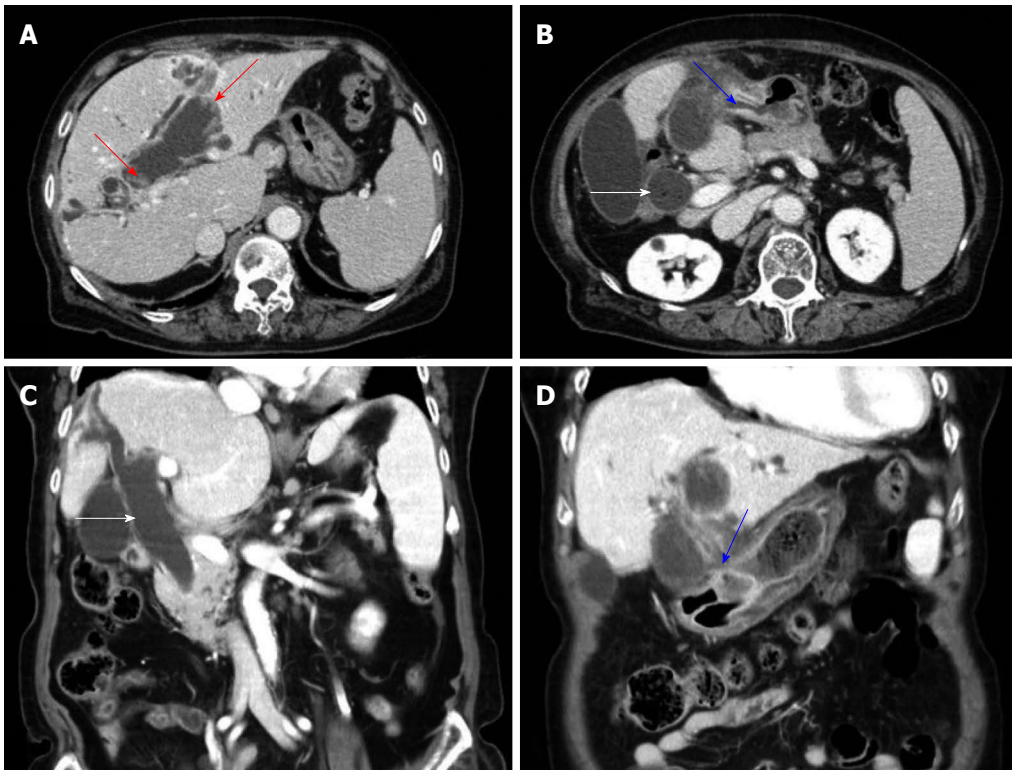

Figure 1 Computed tomography of the abdomen showed markedly dilated common bile duct (white arrows) and left intrahepatic duct with left intrahepatic duct penetrating into the antrum of stomach and fistula formation (blue arrows) and papillary projections along the dilated bile duct (red arrows) and no definite visible mass in the left intrahepatic duct (A-D).

part and to our best knowledge, only two cases of IPMN with the bile duct with one fistula into other organs were reported in the English literature[5,6] and here, we describe the first case of biliary IPMN with two fistulas into the stomach and duodenum.

CASE REPORT

An 87-year-old woman was admitted to our hospital because of acute right upper quadrant abdominal pain. On physical examination, palpable mass and tenderness of upper abdomen was noted. The complete blood count results showed white blood cell count of 3630/mm^3, hemoglobin of 7.8 g/dL, and platelet count of 188000/mm^3. The blood chemistry analysis showed total protein of 8.6 g/dL, albumin of 3.3 g/dL, total bilirubin of 2.7 mg/dL, aspartate aminotransferase of 29 U/L, alanine aminotransferase of 36 U/L, alkaline phosphatase of 249 IU/L, gamma-glutamyltransferase of 105 U/L, creatinine of 0.9 mg/dL, amylase of 45 U/L, and lipase of 35.6 U/L. Serum tumor markers of serum alpha-fetoprotein, CA19-9 and carcinoembryonic antigen were 1.9 ng/mL, < 2.0 U/mL and 7.5 ng/mL, respectively. Computed tomography (CT) of the abdomen showed markedly dilated common bile duct (CBD) and left intrahepatic duct (IHD) with left IHD penetrating into the antrum of stomach and fistula formation and no definite visible mass in left IHD (Figure 1). Endoscopy showed a round ulcerated lesion and extruding white thick mucin from the opening at the lesser curvature of the antrum during endoscopic suction and another wide opening of the fistula with mucin excretion proximal to the original papillary orifice (Figure 2). Cholangiogram obtained from the duodenal fistula near the papillary orifice showed moderately to severely dilated CBD and proximal left IHD with amorphous, partial intraluminal filling of the contrast in the bile duct (Figure 3). The lesion was strongly suspicious of IPMN of the bile duct with combined choledochogastric and choledochoduodenal fistulas. Four days after admission, serum bilirubin increased up to 5.0 mg/dL. Endoscopic suction to extract mucin to relieve jaundice caused by biliary mucinous obstruction and biopsy from the lesion of left IHD were planned using direct peroral cholangioscopy with ultra-slim endoscope (Olympus), but the removal of mucin by endoscopic suction with standard upper endoscope or ultra-slim endoscope was very difficult and failed because of very thick and high viscous mucin (Figure 4). And then, a partially covered metal stent was inserted through the choledochogastric fistula and endoscopic suction through the stent with ultra-slim endoscope also failed due to very thick mucin (blue arrow, Figure 5). Despite of approaching up to common hepatic duct level with ultra-slim endoscope through the choledochoduodenal fistula, target biopsy was not performed due to physical obstacle of large amount of very thick mucin, but instead, specimens were obtained from the proximal site of the fistula near left IHD through the metal stent in choledochogastric fistula and additional biopsy at the distal site of the choledochogastric fistula near the gastric antrum were done. Serum bilirubin level

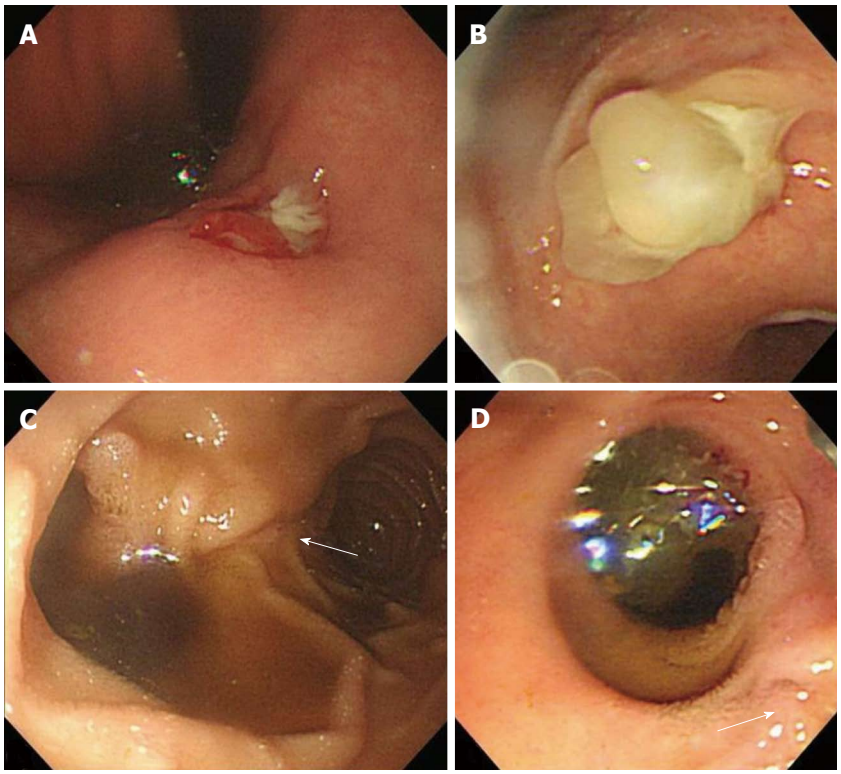

Figure 2 Endoscopic finding showed a round ulcerated lesion (A) and extruding white thick mucin from the opening at the lesser curvature of the antrum during endoscopic suction (B) and another wide opening of the fistula with mucin excretion proximal to the original papillary orifice (white arrows) (C, D).

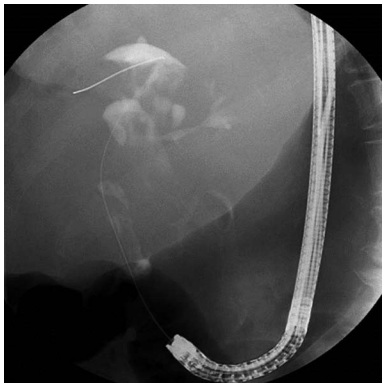

Figure 3 Endoscopic retrograde cholangiopancreatography finding through the choledochoduodenal fistula near the papillary orifice showed moderately to severely dilated common bile duct and proximal left intrahepatic duct with amorphous, partial intraluminal filling of the contrast.

was increased up to 6.0 mg/dL next day, but the patient refused surgical intervention and continued to complain abdominal pain and jaundice.

After insertion of percutaneous transhepatic biliary drainage (PTBD) catheter (Figure 5), the irrigations of N-acetylcysteine (300 mg) *via* the catheter three times a day for 10 d, abdominal pain resolved with decreased serum bilirubin level to 1.0 mg/dL and she was discharged with keeping the PTBD catheter and drainage bag. Pathology showed a low grade dysplasia from the proximal site of the choledochogatric fistula near the left IHD (Figure 6) and non-specific inflammation from the distal site of the fistula near the gastric antrum. She was still alive until recently during the follow-up period of 15 mo.

DISCUSSION

IPMN of the pancreas was first reported by Ohhashi *et al*[7] in 1982 and the clinical features are secretion of large amount of mucin by papillary neoplasm, dilatation of the main pancreatic duct or its branch ducts, slow growth with favorable prognosis, and chronic vague abdominal pain. The pathologic feature of the IPMN of the pancreas reveals the presence of a macroscopic intraluminal lesion and visible mucin on the surface of the tumor with solitary or diffuse intraductal growth[8]. IPMN of the bile duct is a variant of the bile duct malignancy and has a similar clinicopathologic features as its pancreatic counterpart because both the bile ducts and the pancreas develop from the ventral endoderm, although IPMN of the bile duct is associated with higher malignancy rate at the time of surgery than its pancreatic counterpart[9,10]. IPMN sometimes represents expansive progression with mucus extrusion and occasionally make a fistula penetrating into other organs. Fistula formation is divided into two types based on the mechanism, invasive penetration by malignant invasion and mechanical penetration by mucin extrusion with duct expansion[7].

In our case, the choledochogastric fistula formation was highly suggestive of mechanical penetration in that the specimen obtained from the distal part of the fistula near the stomach histologically showed non-specific inflammation, while the proximal part near the left IHD

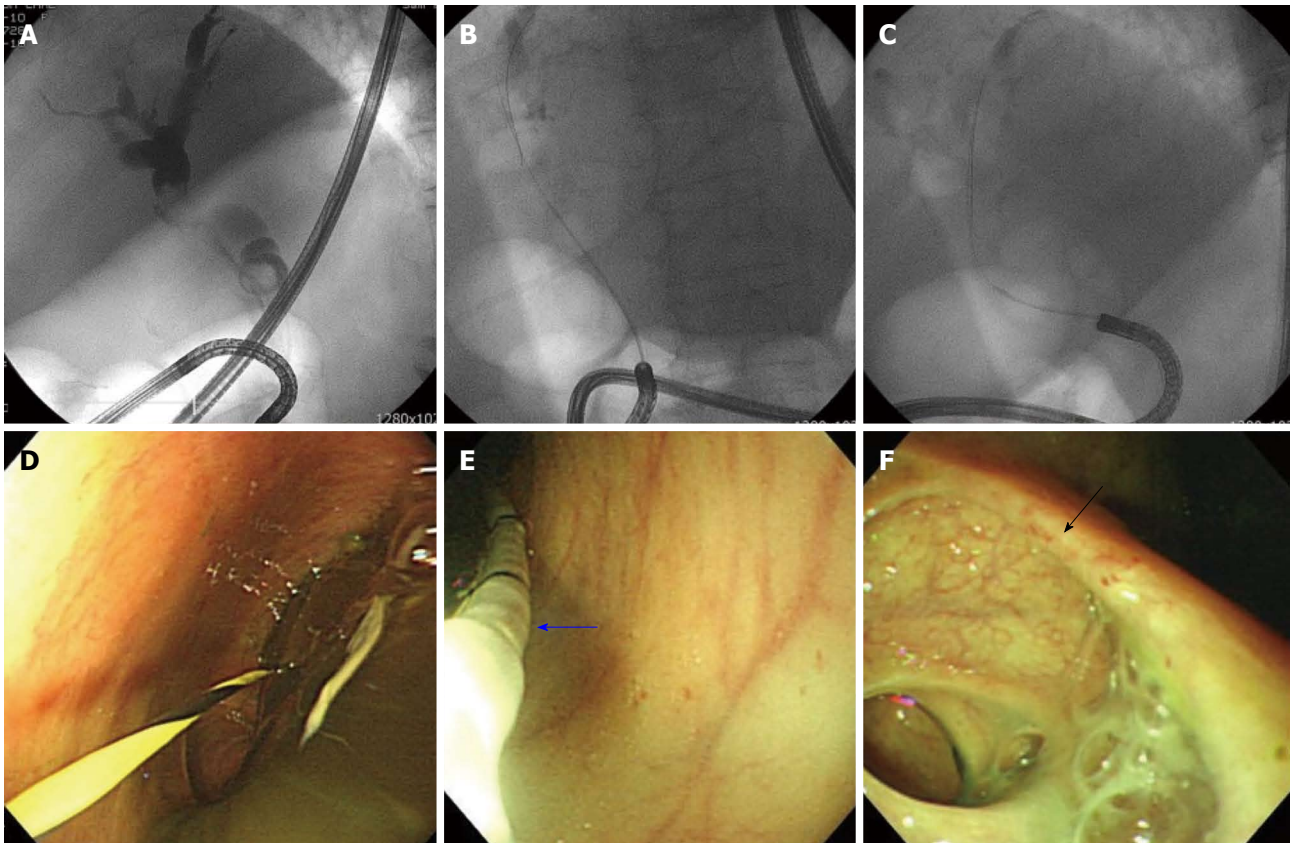

Figure 4 Cholangiogram using ultra-slim endoscope showed moderately to severely dilated common bile duct and both proximal intrahepatic duct with the amorphous, partial intraluminal filling in the bile duct (A-C) and the suction of thick mucus after advancement into bile duct and approach up to the cystic duct (black arrow) level using anchoring of the balloon catheter (blue arrow) was ineffective (D-F).

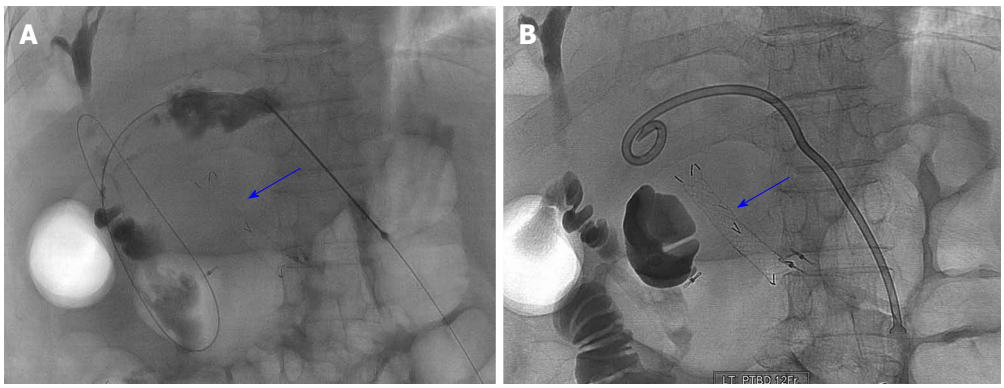

Figure 5 Cholangiogram obtained after contrast injection through the access needle into the left intrahepatic duct showed moderately to severely dilated left intrahepatic duct and common bile duct with the amorphous intraluminal filling consistent with the endoscopic retrograde cholangiopancreatography finding and the metal stent (blue arrow) previously inserted into the choledochogastric fistula for facilitating endoscopic suction of mucin through the stent was in place (A, B).

showed low grade adenoma.

The consensus guidelines for management of IPMN of the pancreas was well established since 2006, meanwhile, there has no published literature for making the accurate diagnosis and proper management of IPMN of the bile duct[11]. Although the majority of malignant IPMN of the bile duct demonstrates tumors or mural nodule in the bile ducts, in some cases the tumor is not visible in images or even in gross specimens and moderately to severely dilatation of the bile duct with mucobilia is the only finding like our case[2]. The diagnosis of IPMN of the bile duct was based on multimodality assessment of various imaging techniques. Ultrasonography is initial examination of biliary dilatation and stenosis with viscous mucin as fine echogenic findings. CT with magnetic resonance imaging have better delineation of biliary dilatation with tumor location, extent and volume (stage). ERCP is a relatively invasive examination

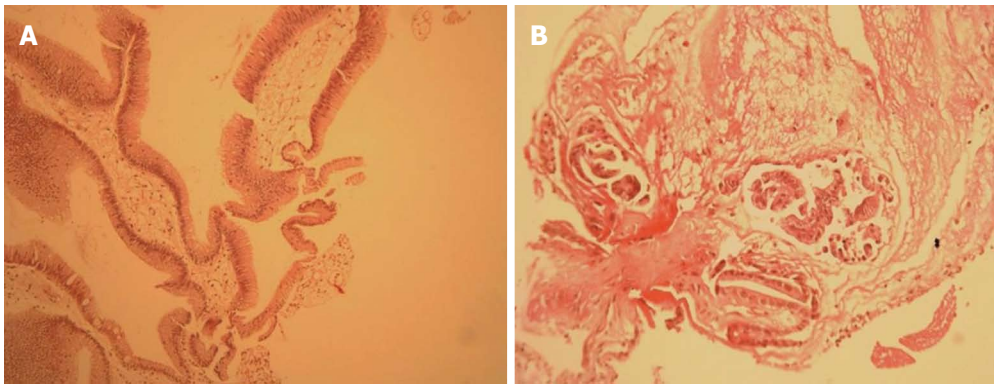

Figure 6 Pathology of the specimen from the proximal portion of the choledochogastric fistula showed a low grade adenoma [hematoxylin and eosin stain, × 200 (left), × 400 (right)].

and shows mucobilia as a filling defect of contrast in bile duct and endoscopic ultrasound (EUS) can be used for detecting mural nodule or solid mass with local invasion and cytological analysis obtained by fine needle aspiration[1,3,11]. EUS examination was not performed in our patient because of no visible mass in the CT and ERCP findings.

The insertion of multiple uncovered metal stents has been shown to be feasible in the patients of IPMN of the pancreas with biliary obstruction by mucoid impaction[12], but the insertion of multiple metal stents alongside each other to facilitate biliary drainage could not apply to the patient of severely dilated bile duct with thick mucoid impaction and no specific stenosis like our case.

The mucolysis of antioxidant N-acetylcysteine (NAC) was widely used in the management of the symptom of the chronic obstructive pulmonary disease and other respiratory conditions such as idiopathic pulmonary fibrosis[13,14] and the usefulness of the dissolution of the renal stone by the irrigation with NAC *via* percutaneous nephrostomy was reported[15]. A case of the effectiveness of infusion of NAC through nasobiliary catheter for advanced biliary IPMN was recently reported[16]. In our case, the bilirubin level and her abdominal pain was improved by the intermittent infusions of NAC (300 mg) three times a day for 10 d through the PTBD catheter. Choledoscopy *via* PTBD after resolution of abdominal pain and jaundice with multiple irrigations of NAC was intended for further detailed examination of IHD, but she denied and only request symptom relief.

In summary, IPMN of bile duct with combined two fistulas into the stomach and the duodenum presented with abdominal pain and ongoing jaundice due to thick mucoid impaction in the bile duct was successfully treated with the irrigation with NAC for 10 d.

COMMENTS

Case characteristics

The patient presented with abdominal pain and jaundice.

Clinical diagnosis

Intraductal papillary mucinous neoplasm (IPMN) of the bile duct with combined fistulas of the stomach and the duodenum.

Differential diagnosis

Mucin-producing cholangiocarcinoma or biliary papilloma(tosis) or papillary cholangiocarcinoma were considered because of mucin hypersecretion and moderately to severely dilation of the bile duct on imaging studies.

Laboratory diagnosis

Acute cholangitis accompanied with IPMN of the bile duct was based on fact that initial serum total bilirubin level was 2.7 mg/dL and reached up to 6 mg/dL six days after admission.

Imaging diagnosis

IPMN of the bile duct with combined fistulas of the stomach and the duodenum was based on multimodality imaging and endoscopic finding.

Pathological diagnosis

Histologic finding of the specimen obtained from left intrahepatic bile duct through the inserted metal stent in choledochogastric fistula showed IMPN of the bile duct with low grade dysplasia.

Treatment

The patient's abdominal pain with jaundice was settled after the multiple irrigations of N-acetylcysteine (NAC) through percutaneous transhepatic biliary drainage (PTBD) catheter for 10 d.

Related reports

Two case reports of IPMN of the bile duct accompanied with choledochoduodenal fistula published in English were shown in references 5, 6.

Experiences and lessons

Clinicians should consider that multiple irrigations of NAC *via* PTBD tube is an alternative therapeutic option for IPMN of the bile duct with thick mucoid impaction accompained with cholangitis after failed endoscopic suction of mucin.

Peer review

The authors presented a rare, interesting case of IPMB with combined fistula formation into the stomach and the duodenum. This case is very interesting.

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