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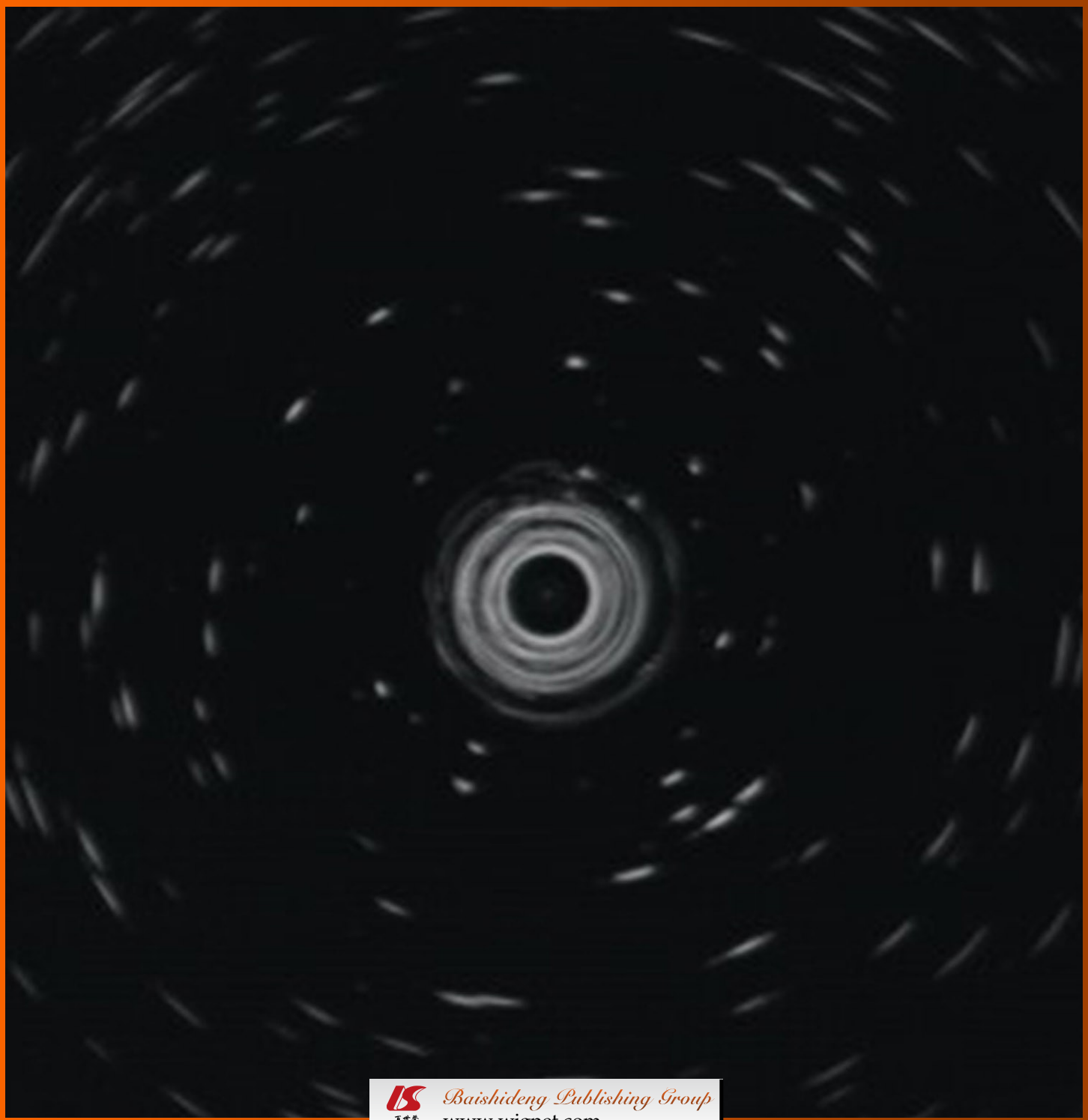

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EDITORIAL

Endoscopy in inflammatory bowel disease when and why

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Abstract

Endoscopy plays an important role in the diagnosis and management of inflammatory bowel disease (IBD). It is useful to exclude other aetiologies, differentiate between ulcerative colitis (UC) and Crohn's disease (CD), and define the extent and activity of inflammation. Ileocolonoscopy is used for monitoring of the disease, which in turn helps to optimize the management. It plays a key role in the surveillance of UC for dysplasia or neoplasia and assessment of post operative CD. Capsule endoscopy and double balloon enteroscopy are increasingly used in patients with CD. Therapeutic applications relate to stricture dilatation and dysplasia resection. The endoscopist's role is vital in the overall management of IBD.

Key words: Colonoscopy; Oesophagogastroduodenoscopy; Capsule endoscopy; Enteroscopy; Ulcerative colitis; Crohn's disease; Dysplasia; Endoscopist

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INTRODUCTION

Endoscopy is a crucial tool in the management of inflammatory bowel disease (IBD). There is a spectrum of situations when an endoscopy may be of value in IBD, extending from initial diagnosis to differentiating between Crohn's disease (CD) and ulcerative colitis (UC) to long term management of both conditions.

Of the several endoscopic tools, colonoscopy remains the prime diagnostic tool. Gastroscopy, enteroscopy and endoanal ultrasound scan may be useful in the assessment of specific organ involvement in CD and to differentiate between UC and CD. Novel tools such as capsule endoscopy and double balloon enteroscopy have been playing an increasing role for small bowel Crohn's disease assessments. Both CD and UC can be complicated by primary sclerosing cholangitis (PSC): ERCP previously the gold standard to diagnose PSC has broadly been superseded by magnetic resonance cholangiopancreatography[1]. This article will focus on the role of colonoscopy in IBD as this is by far the most important tool. A brief overview of other endoscopic tools will follow.

COLONOSCOPY

Over the years, improvements in colonoscope technology have led to more comfortable procedures with better quality image definition (namely narrow band imaging, chromo endoscopy, endomicroscopy and high definition screens)[2]. Training in colonoscopy has optimised the

Table 1 Infective causes of inflammation which mimic inflammatory bowel disease

Infective cause	Endoscopic appearance
Salmonella	Friable mucosa with haemorrhages in ileum and colon
Shigella	Patchy intense erythema in ileum and colon
Campylobacter	Erythema and ulcers in colon
E.coli 0157:H7	Mild to moderately severe colitis
Yersinia	Patchy colitis with ileal aphthoid ulcers
C.difficile	Pseudo membranes and predominantly left side colitis
Klebsiella	Haemorrhagic colitis
Mycobacterium	Transverse or circumferential ulcers ileum
Neisseria	Proctitis with ulcers and peri anal disease
Chlamydia	Peri anal abscess, ulcer and fistula
Treponema	Proctitis with ulcers and peri anal disease
Schistosoma	Extensive colitis, may be segmental with polyps
Entamoeba	Acute colitis and ulcers
Herpes	Proctitis with rectal ulcers and perianal disease
Cytomegalovirus	Colitis with punched out shallow ulcers
Aspergillus	Ulcers with bleeding
Histoplasma	Predominantly right side colitis

use of this instrument for various diagnostic purposes. Colonoscopy remains the first line endoscopic investigation for suspected CD. Flexible sigmoidoscopy offers a diagnostic option for UC, with colonoscopy reserved to define the disease limit in some cases. The role of colonoscopy in the management of IBD can be summarised as follows[3,4]: (1) to establish a diagnosis; (2) to assess the disease extent and activity; (3) to monitor disease activity; (4) for surveillance of dysplasia or neoplasia; (5) to evaluate ileal pouch and ileorectal anastomosis; (6) to provide endoscopic treatment, such as stricture dilation/stent placement.

COLONOSCOPY AS A DIAGNOSTIC TOOL

One of the pitfalls in diagnosing IBD is the failure to consider other diseases, which may give terminal ileal and colonic inflammation. By far the commonest cause of inflammation is infection. Infective causes[5] are outlined in Table 1; the typical features to assist diagnosis are also described. Other conditions that may mimic IBD[6] with colonic and terminal ileum (TI) inflammation are summarised in Table 2.

Once these conditions have been excluded there remains the challenge of differentiating between CD and UC. This activity has important implications for disease management and prognosis. Whilst most cases are straightforward, around 5% of cases particularly with colitis, final diagnosis is evasive and the disease is defined as unclassified IBD[7].

Features of UC

The endoscopic findings of active UC range from erythema, loss of the usual vascular pattern due to oedema, granularity of the mucosa and friability/spontaneous bleeding to erosions/ulceration[8] (Figures 1 and 2).

The ulceration in UC has typical features: superficial ulcers, which may coalescence to large ulceration extending circumferentially. By virtue of the continuous inflammatory nature of UC, ulcers always surrounded by inflamed mucosa (Figure 3).

Table 2 Non infective causes of diarrhoea

Inflammatory	Behcet's disease
Drugs	Non streroidal anti inflammatory drugs
	Gold
	Penicillamine
Iatrogenic	Radiation colitis
Vascular	Vasculitis
	Ischaemic colitis
Neoplastic	Colorectal cancer

Distribution of the inflammation may be helpful in differentiating between UC and other causes of colitis particularly Crohn's colitis. Rectal involvement is invariable with continuous disease extending proximally. Recognised variations to this pattern include rectal sparing, particularly if patients have been using topical therapy, and peri-appendiceal inflammation. Small bowel involvement may occasionally be present in the form of backwash ileitis. This appearance differs from CD: diffuse continuous erythema with no ulceration compared to typical Crohn's appearance[9]. Endoscopic mucosal appearance alone might underestimate the extent when compared to the histological involvement.

Chronic UC may display quiescent disease but changes of previous activity such as post-inflammatory polyps (Figure 4) scarring (Figure 5) and a shortened tubular colon (Figure 6) may be evident. Strictures are rare in UC; its presence heralds a fivefold risk of colorectal cancer (CRC) and such patients should be followed up with care[10].

Disease extent and activity influence medical management: this is reflected in the choice of medical therapy and the route of administration as well as risk stratification of colonic cancer[11]. Hence the importance of recording these finding in endoscopic report cannot be underestimated. Disease extent is recorded as the extent of inflammation from the anal verge; mucosal involvement is not static it can progress or regress over time[12]. Disease activity is recorded as mild, moderate or severe with more than 12 disease activity scoring systems reported in the literature[13]. Commonly used endoscopic indices[14-18] are summarised in Table 3. The score used in most drug studies is the Mayo endoscopic score of activity. The Mayo score ranges from 0 to 12, with higher scores corresponding with more severe disease[19]. An "optimal" scoring instrument for UC is still to be developed and will require validation before extensive use in clinical trials can be promoted[13].

Features of Crohn's disease

Inflammation in CD can involve the entire gastrointestinal tract; 40%-55% of cases show inflammation in the terminal ileum and colon, 15%-25% colonic inflammation alone and in 25%-40% ileum is exclusively

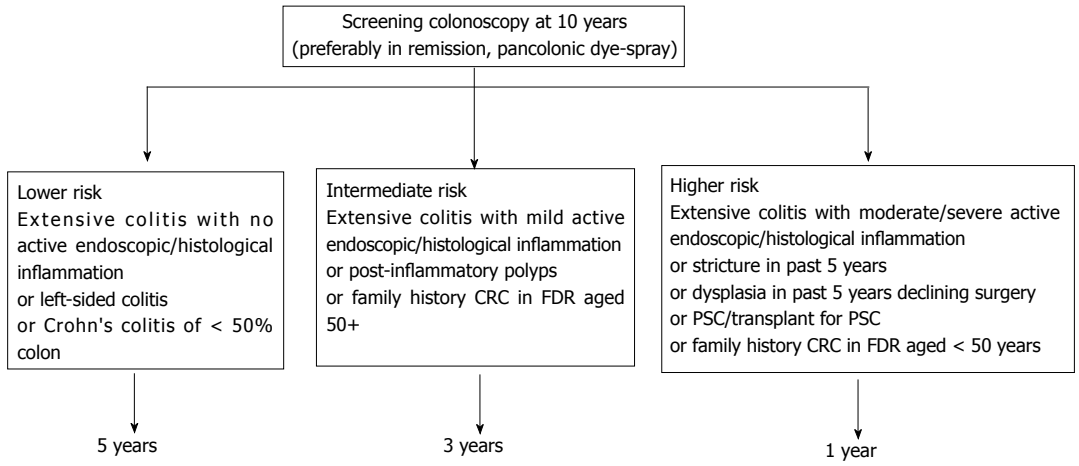

Figure 1 British Society of Gastroenterology guidelines on surveillance of colitis. PSC: Primary sclerosing cholangitis; CRC: Colorectal cancer.

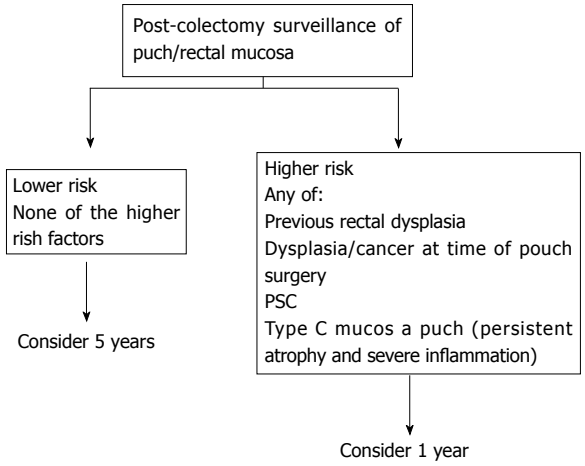

Figure 2 British Society of Gastroenterology surveillance recommandations post colectomy. PSC: Primary sclerosing cholangitis.

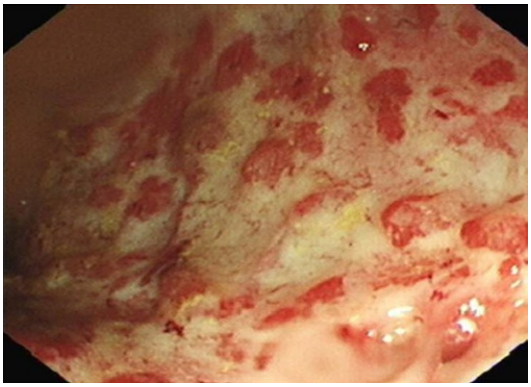

Figure 3 Severe colitis (Sutherland score 3). Friable, granular mucosa with exudates overlying the surface, ulcers and sub mucosal oedema of rectum.

involved[20]. Involvement of oesophagus, stomach and proximal small bowel occurs in up to 10% of CD patients. The rectum is spared in up to 50% patients with colonic disease[6].

The endoscopic hallmark of CD is the heterogeneous patchy nature of inflammation or skip lesions (areas of inflammation interposed between normal mucosa). Ulceration in CD commonly occurs on a background of minimal inflammation[5].

CD ulcers tend to be longitudinal, polycyclic ulcers (snail track) associated with cobblestone appearance of ileum, fistulous tract and strictures either in the colonic or ileum. Circumferential inflammation is rare in CD. The ulcers are deep when compared to superficial ulcers in UC[6] (Figure 7).

The presence of small ulcerations on the ileocaecal valve or within the TI in a symptomatic individual is highly suggestive of CD (Figure 8); the possibility of tuberculosis and nonsteroidal antiinflammatory drug induced ileal ulcers should be considered[21,22]. Young people may have benign aphthous ulceration related to lymphoid hyperplasia which should not be diagnosed as CD[23].

Several activity indices for CD are in use. Most of them are complicated and time consuming. A simple scoring system suitable for clinicians is the simple endoscopic score of CD (SES-CD) which came into use recently. Table 4 summarises the features of SES-CD[24].

Biopsy specimens should be taken from ulcerated mucosa as well as from normal mucosa adjacent to inflammatory areas, in order to demonstrate the skip phenomenon. Biopsy specimens taken from the edges of ulcers and aphthous erosions maximize the yield of identifying granulomas. The practice of collecting biopsies from macroscopically normal rectal mucosa allows the differentiation between a diagnosis of UC in suspected colonic CD[21,22,25]. Table 5 summarises the prime endoscopic differences between UC and CD[26].

MONITORING DISEASE ACTIVITY

The use of colonoscopy as a diagnostic tool is non-contentious. Its value in disease monitoring is an evolving indication for the procedure. The thrust in this direction comes from the more recent focus on mucosal healing or reducing inflammatory activity in IBD. The prognostic implications of mucosal healing include reduced sur-

Table 3 Endoscopic indices used in ulcerative colitis

	0	1	2	3	4
Sutherland	Normal	Mild friability	Moderate friability	Exudates and spontaneous haemorrhages	-
Schroeder	Normal or inactive disease	Mild (erythema, decreased vascular pattern)	Moderate (marked erythema, absent vascular pattern)	Severe (spontaneous bleeding, ulceration)	-
Baron	Normal: matt mucosa, ramifying vascular pattern, no spontaneous bleeding/to light touch	Abnormal, but non-haemorrhagic: appearances between 0-2	Moderately haemorrhagic: bleeding to light touch, but no spontaneous bleeding	Severely haemorrhagic: spontaneous bleeding and bleeds to light touch	-
Feagan	Normal, smooth, glistening mucosa, with normal vascular pattern	Granular mucosa; vascular pattern not visible; not friable; hyperaemia	As 1, with a friable mucosa, but not spontaneously bleeding	As 2, but mucosa spontaneously bleeding	As 3, but clear ulceration; denuded mucosa
Powel- Tuck	Non haemorrhagic, no spontaneous bleeding or bleeding to light touch	Haemorrhagic, no spontaneous bleeding, but bleeding to light touch	Haemorrhagic, spontaneous bleeding ahead of instrument at initial inspection with bleeding to light touch	-	-
Lemann, Hanauer	Normal mucosa	Oedema, +/- loss of vascular pattern, granularity	Friability, petechiae	Spontaneous haemorrhage, visible ulcers	-

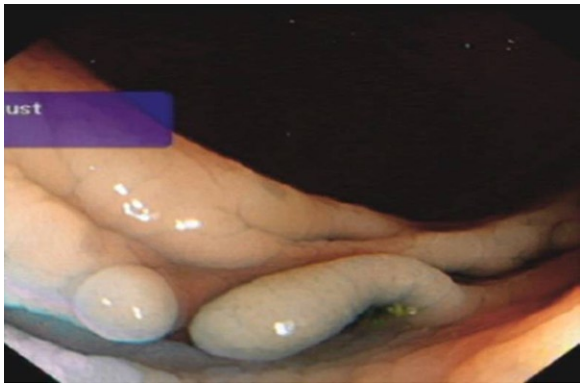

Figure 4 Post inflammatory polyp in transverse colon in a patient with ulcerative colitis.

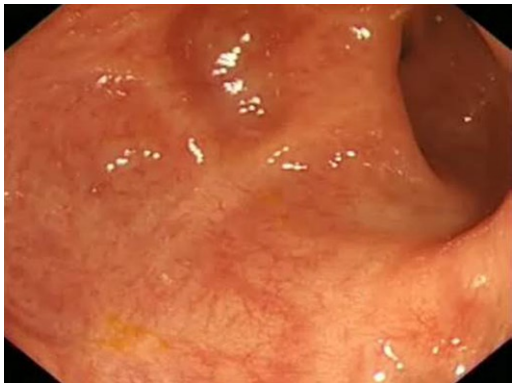

Figure 5 Extensive scarring of sigmoid colon in a patient with long history of colitis.

gical intervention[27], prolonged remission[27], and reduced risk of colorectal cancer[10].

Patients with quiescent disease may have a relatively normal appearing mucosa with a distorted vascular pattern but without friability. Mild disease might appear oedematous and granular with distortion of the vascular markings, moderate activity is defined by the presence of a coarse granular pattern, erosions and friability of the mucosa. Severe disease displays gross ulcerations and areas bleed spontaneously[5]. The presence of severe ulceration is usually associated with refractory disease and increased frequency of complications such as perforation[5].

SURVEILLANCE FOR DYSPLASIA OR NEOPLASIA

Several studies have reported an increased risk for colorectal cancer in UC and Crohn's colitis. This risk has been examined with respect to disease duration and extent[28,29]. The cumulative risk for colorectal cancer was estimated as 1.6%, 8.3% and 18.4% after 10, 20 and 30 years of disease respectively[28]. The associated risk for extent was reported in a population based study as standardised incidence ratio of 2.8 for left sided colitis and 14.8 for pan-colitis[30]. Risk assessment of CRC also critically relies on endoscopic appearance of the severity of disease activity: both endoscopic and histological inflammation was shown to be associated with increased risk[10,31]. Conversely, in a macroscopically normal colonoscopy the associated cancer risk was observed to be similar to age and sex-matched controls[10]. PSC is an independent risk factor for cancer with an odd ratio for developing cancer of 4.49 (95% CI: 3.58-6.41) compared to patients without PSC[32].

As a consequence of the above observations, colonoscopic surveillance for neoplasia is recommended by most gastroenterology and endoscopic societies. The purpose of surveillance colonoscopy is to identify early pre-malignant lesions indicative of an enhanced risk of CRC. The original literature focused on dysplasia-associated lesions/masse (DALM), however we now have evidence that neoplasia may be flat and subtle. The endoscopic techniques for improving dysplasia detection are discussed here in the later section.

FLEXIBLE SIGMOIDOSCOPY

One of the limitations of colonoscopy is the need for

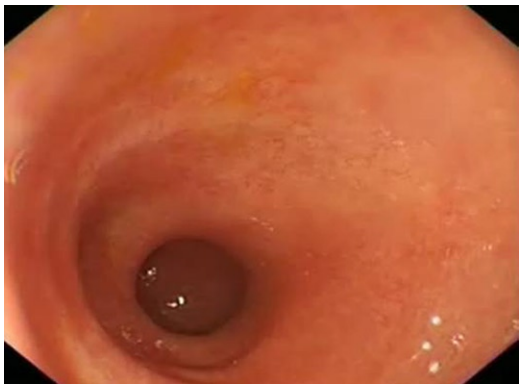

Figure 6 Shortened tubular colon in a patient with pan colitis.

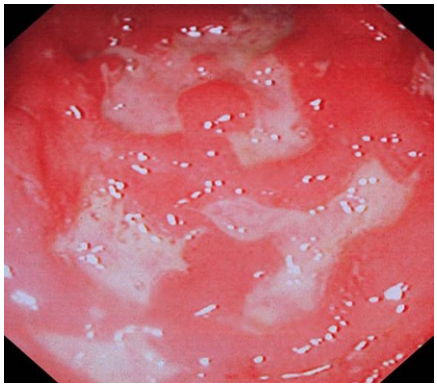

Figure 7 Deep ulcers, sub mucosal oedema and haemorrhages in the sigmoid colon in a patient with Crohn's colitis.

oral bowel preparation to enhance adequate mucosal views. In some situations a limited examination of the left colon with flexible sigmoidoscopy may suffice. The procedure may be undertaken following an enema or sometimes-unprepared procedure. Sigmoidoscopy provides useful information in many situations particularly: (1) when colonoscopy is considered high risk or contraindicated e.g., acute severe colitis or fulminant colitis[13]; (2) to define the severity of the disease in established colitis; (3) to exclude superimposed infection with cytomegalovirus (CMV) and C.Difficile; (4) to exclude other causes for symptoms when there is poor response to therapy e.g., ischaemic colitis.

OESOPHAGO-GASTRODUODENOSCOPY

Oesophagogastroduodenoscopy (OGD) in suspected IBD are recommended in paediatric population where differentiating between UC and CD can be challenging[33]. In adult IBD, there are no specific recommendations. Symptoms of dyspepsia, abdominal pain, vomiting or findings of nutritional deficiency in CD warrant an OGD. Upper gastrointestinal (GI) tract involvement occurs in up to 13% of patients with CD[34]. Moreover a minority of UC patients may also have upper GI tract inflammation, manifesting as diffuse duodenitis or gastritis, characterised by oedema, erythema, erosions, and thickened mucosal folds[35]. OGD with small bowel biopsy in patients with IBD include evaluation of concomitant coeliac disease and small bowel adenocarcinoma[36]. There are therapeutic applications of OGD in patients suffering from CD; symptomatic duodenal or pyloric strictures (Figure 9) can be successfully treated with endoscopic balloon dilation[37] (Figure 10).

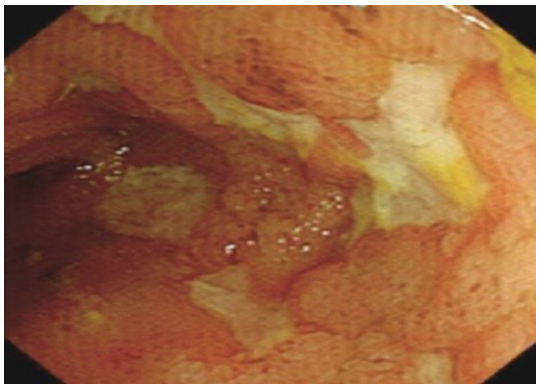

Figure 8 Multiple linear, deep ulcers with normal islands of intervening mucosa in the terminal ileum indicates severe Crohn's disease.

Table 4 Simple endoscopic score for Crohn's disease

Variable	Simple endoscopic score			
	0	1	2	3
Size of ulcers	None	Aphthous ulcers	Large ulcers	Very large ulcers
Ulcerated surface	None	< 10%	10%-30%	> 30%
Affected surface	Unaffected segment	< 50%	50%-75%	> 75%
Presence of narrowing	None	Single, scope passable	Multiple, scope passable	Scope impassable

Table 5 Differences in the macroscopic appearance between Crohn's disease and ulcerative colitis

Macroscopic features	UC	CD
Erythema	+++	++
Loss of vascular pattern	+++	+
Granularity of mucosa	+++	+
Cobble stone appearance	-	++
Pseudo polyps	+++	+++
Aphthous ulcers	+	+++
Deep ulcers	-	+++
Patchy inflammation	-	+++
Ileal ulcers	-	+++
Rectal involvement	++++	++

UC: Ulcerative colitis; CD: Crohn's disease.

CAPSULE ENDOSCOPY

Small bowel capsule endoscopy (SBCE) was first introduced in 2001. Over the last decade it has evolved as a sensitive modality for the detection of small bowel

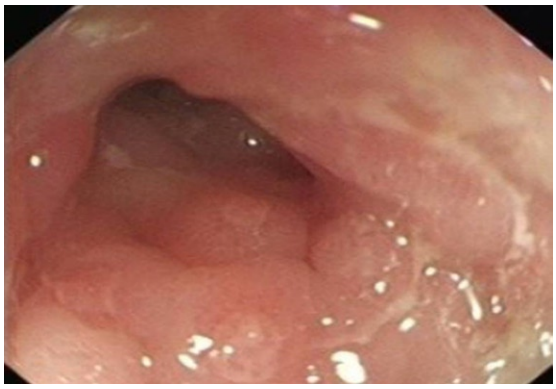

Figure 9 Linear pyloric ulcer and surrounding sub mucosal oedema-pyloric Crohn's disease.

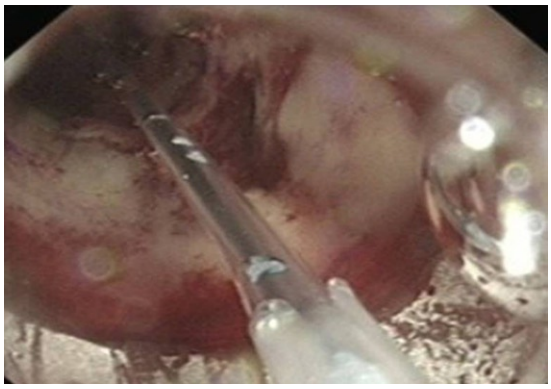

Figure 10 Balloon dilatation of Crohn's stricture.

lesions including CD. The main advantage of SBCE is the potential to visualise the entire length of the small bowel. It is less invasive and better tolerated. When compared to radiological investigations (CT or MR enterography) it is very sensitive to detect early mucosal lesions. Recent study showed the sensitivity for diagnosis of CD of the terminal ileum 100% by SBCE, 81% MR enterography, and 76% by CT enterography, respectively[38,39].

Recent meta-analysis suggested that SBCE has the highest diagnostic yield in non-stricturing CD (69% SBCE *vs* 30% small bowel Barium follow through) and is significantly superior to the conventional endoscopy or CT/MR enterography for lesion detection. It is particularly useful in patients with established CD to detect disease recurrence[40]. There are drawbacks of SBCE. The main disadvantage is the lack of tissue sampling option. Non-diagnostic mucosal abnormalities may thereafter need to be followed by more invasive (enteroscopy) procedures for histological sampling. Additional drawbacks include obscured view due to debris, non-suitability for patients with delayed transit and the risk of capsule retention in severe stricturing disease[40].

Despite the limitations experts propose capsule endoscopy for monitoring of patients with known diagnosis of Crohn's disease and in detecting post surgical disease recurrence[41,42]. Costs and availability may however mitigate its value in repetitive testing.

ENTEROSCOPY

Double balloon enteroscopy allows a more complete evaluation of the small intestine than single balloon enteroscopy[43-45]. It complements capsule endoscopy particularly when the diagnosis of IBD is uncertain and biopsies are required and for therapeutic interventions namely dilation of small bowel strictures[43,44].

A recent study examined the value of intra-operative enteroscopy to define mucosal inflammation extent as a means of minimising resection length[46]. Intra operative small bowel endoscopy was performed on 33 occasions in 31 patients with CD to compare intraluminal to external inflammation. Endoscopic findings influenced surgical decisions on 20 of the 33 occasions reducing the length of planned resection in 14 cases.

ROLE OF ENDOSCOPY IN SPECIAL SITUATIONS

Endoscopic surveillance

Surveillance for CRC is indicated for patients with IBD: the risks for UC are similar to Crohn's colitis of equal colonic extent and disease duration. Endoscopic appearances are a valuable predictor of future dysplasia and CRC[2]. Rutter *et al*[10] showed that post-inflammatory polyps, strictures, shortened colons and tubular colons were associated with increased risk for future neoplasia with respective odds ratios of 2.14 (95% confidence interval 1.24-3.70), 4.22 (1.08-15.54), 10 (1.17-85.6) and 2.03 (1.00-4.08). No significant association was found with the presence of backwash ileitis, scarring, or a featureless colon.

The British Society of Gastroenterology (BSG) guidelines propose that patients with UC or Crohn's colitis should have a colonoscopy 10 years after the initial diagnosis to define the extent and activity of the disease[7]. Surveillance colonoscopy should be undertaken preferably in remission. The following risk factors dictated the risk and frequency of future surveillance procedures: disease duration and extent associated primary sclerosing cholangitis, family history of sporadic colorectal cancer, young age at diagnosis and endoscopic and histological appearance during colonoscopy[5,9,10]. Screening interval depends on the above risk factors and according to the national and international guidance. Figures 1 and 2 illustrates the summary of current BSG guidelines[7].

Several studies have shown improved detection rates for dysplasia and cancer if targeted biopsies are taken rather than random biopsies[10]. This approach may serve to mitigate the poor clinician compliance to endoscopic protocols for random biopsies every 10 cm[47]. Narrow band imaging has been shown to be no better than standard white light colonoscopy and hence cannot be recommended as an alternative to chromo endoscopy[7]. Although confocal endomicroscopy may enhance the

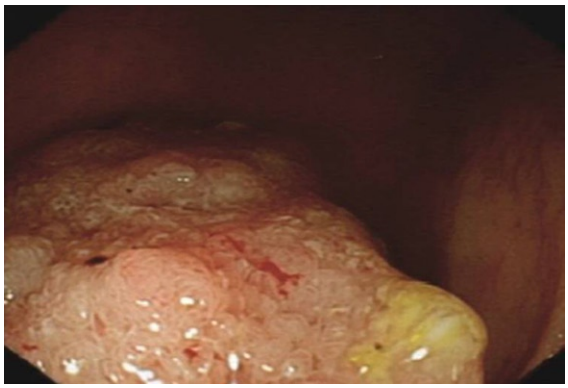

Figure 11 Dysplasia-associated lesions/masse in caecal pole in a patient with a long history of pancolitis.

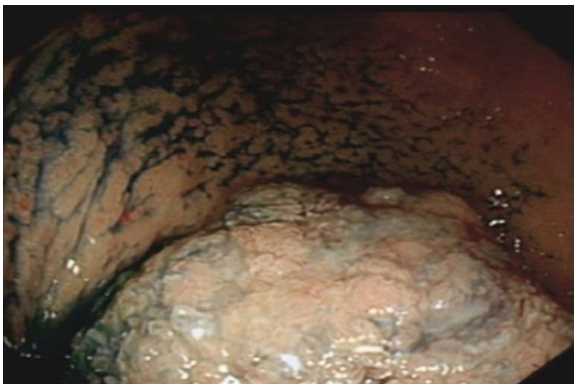

Figure 12 Dysplasia-associated lesions/masse in caecal pole after dye spray.

in vivo characterisation of lesions, it requires prior lesion detection by other means before confocal endomicroscopy can be deployed[2]. Therefore pan colonic dye spray (either with methylene blue or indigo carmine) with targeted biopsies is now recommended[7]. Intuitively such an approach may be expected to be time consuming however the colonoscopy duration was not shown to differ to standard colonoscopy[10]. A recent study by Saunders *et al*[48] described a time-saving technique using a washer pump for dye spray application: indigo carmine was successfully applied to the entire mucosal surface and reduced the procedural time by several minutes while optimising mucosal views and biopsy access.

Most cancers arise with pan colitis; there is little or no increased risk associated with proctitis and left-sided colitis carries an intermediate cancer risk[13]. There is evidence to indicate that colorectal cancer is also more likely to develop with persistent colonic inflammation even in microscopic level[2]. Hence, active inflammation noted at surveillance colonoscopy, is an indication for escalation of medical treatment.

When a dysplastic polyp is detected, it is essential to biopsy the adjacent flat mucosa at the base of the dysplastic polyp to assess the extent of disease and also to detect dysplasia in the surrounding (macroscopically normal) flat mucosa. This may help to differentiate between adenoma-like lesions (ALM) or the traditionally described DALMs[49] (Figures 11 and 12). The swathe of literature pertaining to the management of dysplastic lesions has been summarised in several review articles and lies beyond the scope of this article.

Endoscopic assessment of pouchitis

Pouchitis has been reported as a complication of restorative proctocolectomy for UC in as many as 40%-50% of patients[50]. There are no specific symptoms and signs for pouchitis, which may be similar to other pouch complications such as cuffitis, irritable pouch and CD of the pouch. Furthermore, severity of symptoms does not always correlate with the endoscopic or histological findings and the disease activity is variable with time. Therefore a cumulative assessment of clinical, endoscopic and histological assessment is needed to make the diagnosis of pouchitis[51,52].

Pouch endoscopy (pouchoscopy) provides crucial information with respect to the severity and extent of mucosal inflammation, pre-pouch ileitis and CD of pouch and cuffitis. It also demonstrates other abnormalities such as polyps, strictures, sinuses and fistula. Supplemental information from histology may reveal granulomas, CMV inclusion bodies and dysplasia[51,53-59]. Several diagnostic criteria are available and the commonest in clinical use is the pouch disease activity index[60].

Postsurgical crohns disease

Ileal or ileocolonic CD (Montreal L1 or L3) affects 75% of the Crohn's population[6,20]. In this selected group of patients remission may be achieved by medical or surgical means with a right hemi-colectomy. The latter procedure may also be required for complications particularly strictures and penetrating disease with fistula formation.

Disease recurrence in the neo-terminal ileum is invariable. Rutgeerts' group reported endoscopic, clinical and surgical recurrence rates of 73%, 20% and 5% at 1 year respectively[12]. We reported similar rates at our centre for clinical and surgical recurrence in a retrospective series of 99 patients following surgery (28% clinical and 5% surgical recurrence at 1 year)[61]. The Rutgeerts scoring system is proposed as a means to predict post-surgical recurrence risk[62] (Table 6). The predictability of future clinical recurrence was based on neo-terminal ileal endoscopic appearances (Figure 13) at one year, with a greater risk for scores > i2[12].

Other clinical and histological risk factors for disease recurrence have been identified. The evidence for smoking is the most compelling[63]. Additional clinical factors are disease behaviour with perforating disease and previous resection for CD. Plexitis in the proximal margin of resection specimens implies more aggressive disease and greater recurrence risk[64].

Post-surgical colonoscopic examination of ileocolonic anastomosis (Figure 14) is a valuable predictor for risk of recurrence and may identify patients in need of medical therapy escalation. The optimal time interval

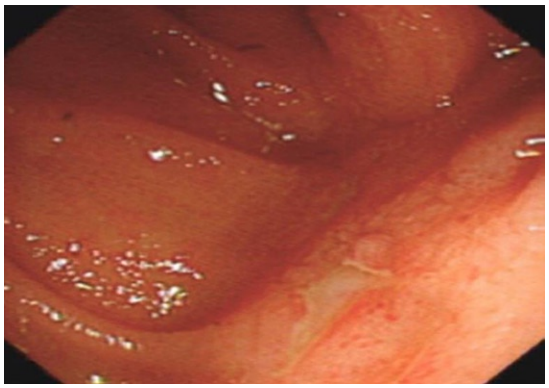

Figure 13 Aphthous ulcer in the neo terminal ileum in a patient who had ileorectal anastomosis(indicates recurrence of Crohn's disease). Note healthy surrounding mucosa.

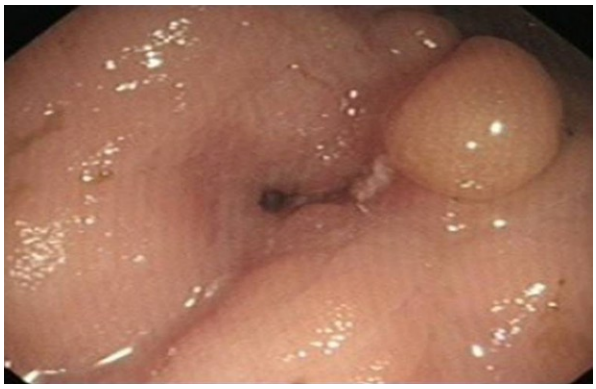

Figure 14 Pin hole stricture in the neo terminal ileum (Crohn's disease).

between surgery and colonoscopy is not known. At our centre we undertake the first colonoscopy at 6 mo. We also proposed a risk stratification of patients based on their risk, with prophylactic medical therapy directed at the risk[65-70]. Figure 3 illustrates the proposed postoperative surveillance strategy.

ROLE OF THE ENDOSCOPIST

Ultimately, it is the endoscopist's interpretation of endoscopic findings that underpins clinical decisions and not endoscopic technological advances. Other than the appropriate choice of endoscopic test to answer the relevant clinical questions, there is an additional responsibility on the endoscopist to recognise and comprehensively record mucosal abnormalities. By assimilating these findings with the clinical presentation a diagnosis is often achieved and a management plan generated. Emphasis on clear, accurate and systematic reporting is paramount particularly when the endoscopist is not the treating physician. Therefore to ensure accurate communication of findings, a simple check list for reporting diagnostic or prognostic colonoscopies should include the following descriptions.

Table 6 Rutgeerts scoring system to monitor post surgery Crohn's disease activity

Score	Endoscopic features
i0	Absence of any lesions at anastomosis and in the neo terminal ileum
i1	Less than 5 aphthous ulcers (< 5 mm)
i2	More than 5 ulcers with normal intervening mucosa or large patchy lesions, or lesions confined to anastomosis (< 1 cm)
i3	Diffuse aphthous ileitis with diffuse inflammation of the ileal mucosa
i4	Diffuse ileitis with large ulcers, nodularity and stenosis.

Mucosal appearance

Appearance should be described in detail focusing on loss of vascular pattern, ulcers size, depth and extent of circumference, haemorrhages and fistula. Distribution of abnormal mucosa should include description of continuous or patchy inflammation, rectal and non-rectal involvement, peri-appendiceal involvement and TI changes.

Disease extent

Describe the extent of disease involvement for instance in UC it is expressed as inflammation distance from the anal verge and in CD length of inflamed segments.

Image labelling

Capture appropriate images of abnormal mucosa and label correctly.

Specimen collection

Collect and correctly label histology specimen. Ensure adequate number of biopsies are taken to increase the yield of histological diagnosis: current consensus is at least two biopsies from five sites including ileum and rectum[7]. Biopsies should be taken from areas of inflammation and the adjacent mucosa proximal to the area of inflammation.

When colonoscopy is undertaken for refractory or acute severe disease the following points must be considered: Alternative diagnosis (ischemia, drug induced, vasculitis, un-related infection); Complications of CD or UC (CMV or Clostridium difficile colitis or neoplasia or fistula formation).

Finally, good communication between endoscopist and histopathologist is mandatory for final decision on diagnosis. This may be achieved through regular multidisciplinary team meeting or attaching the detailed colonoscopy report to all pathology requests.

CONCLUSION

Colonoscopy is one of the most important diagnostic and prognostic tools in the diagnosis and management of IBD. Other endoscopic procedures usually supple-

ment colonoscopy for additional information or treatment of the disease. Management relies on interpretation of endoscopic findings, therefore good knowledge of the various mucosal appearances, descriptions and the implication of each finding, with careful attention to recording each finding is crucial to the optimal management of patients. Surveillance roles for colonoscopy involve optimising the procedure particularly in cancer surveillance and post-operative CD. Therapeutic applications of endoscopy are related to excision of dysplastic lesions and dilatation of strictures.

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EDITORIAL

NOTES, MANOS, SILS and other new laparoendoscopic techniques

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Abstract

A new way of opening a body cavity can be a revolution in surgery. In 1980s, laparoscopy changed how surgeons had been working for years. Natural orifice translumenal endoscopic surgery (NOTES), minilaparoscopy-assisted natural orifice surgery (MANOS), single incision laparoscopic surgery (SILS) and other new techniques are the new paradigm in our way of operating in the 21st century. The development of these techniques began in the late 90s but they have not had enough impact to develop and evolve. Parallels between the first years of laparoscopy and NOTES can be made. Working for an invisible surgery, not only for cosmesis but for a less invasive surgery, is the target of NOTES, MANOS and SILS performed by surgeons and endoscopists over the last 10 years. The future flexible endoscopic platforms and the fusion between laparoscopic instruments and devices and robotic surgery will be a great advance for "scarless surgery".

BEGINNING OF A SURGICAL REVOLUTION: ENDOSCOPIC AND LAPAROSCOPIC SURGERY

Modern endoscopy began in 1805, when Phillip Bozzini first used a system to visualize the inside of the rectum and bladder through a mirror, a candle and a double-lumen ureteral catheter. The first source of inner light was invented by Bruck[1] in 1867 for examining the mouth using an electrical resistance with a platinum filament as a light source.

In 1878, Maximilian Carl-Friedrich Nitze introduced the first working cystoscope that contained a prismatic lens system and a channel through which you could insert a ureteral catheter, conducted in collaboration with Joseph Leiter. After the invention of the incandescent light lamp by Thomas A Edison in 1880, the endoscope became more practical. With the arrival of the twentieth

century, cystoscopy and other studies of open cavities such as esophagoscopy, laryngoscopy and proctoscopy were well established.

In 1909, Hans C Jacobeus conducted the first human laparoscopies and thoracoscopies. In 1918, the importance of pneumoperitoneum was recognized after Goetze's works of his inflating needle. In 1938, Janos Veress developed a needle with a safety tip for the practice of therapeutic pneumothorax in tuberculosis. The cold light was a term used for several years before the fiber optic and light cables were in use. In 1953, Hopkins[2] led the invention of the cylindrical lenses system, which provided images with a greater clarity, brightness and color. The real advances in instrumentation and techniques of laparoscopic surgery were made by Kurt Semm in the mid 60s to the 80s when developing an automatic insufflator with a pressure monitor and a lot of devices for laparoscopy[3]. Familiar with Semm's works, Erich Mühe took interest in surgery of the gallbladder and designs a new laparoscope, called the "Galloscope". The tube diameter was larger and had a system for indirect vision and valves that prevent the loss of gas. On September 12th, 1985, Mühe performed the first laparoscopic cholecystectomy in the world.

Throughout this time, laparoscopic visualization was restricted exclusively to the surgeon. The greatest advance in this field was the development and coupling of the mini video-camera in 1987, which allowed assistants to observe surgeries and help more efficiently. Thus, in 1987, Philippe Mouret performed the first video-laparoscopic cholecystectomy. In subsequent years, Dubois published the first series of laparoscopic cholecystectomies and performed a great laparoscopic activity, developing new techniques such as vagotomy in the treatment of ulcer in 1989[4]. Other pioneers of video-laparoscopic surgery are John B McKernan, WB Saye, Eddie Joe Reddick and Douglas Olsen (United States), Sir Alfred Cuschieri and Leslie K Nathanson (United Kingdom) and Jackes Perrisat (France)[5,6].

Parallel to the development of the clinical implementation of the laparoscopic approach to organs like the spleen, adrenals and stomach, mini-laparoscopy or acuscopic surgery was developed. This form of minimally invasive surgery attempts to make the least number of hits on the abdominal cavity using smaller diameter instrumentation. Instruments and 2.8 mm and 3 mm optics, which allow the same actions with an acceptable view, reproduce conventional laparoscopy with minimal parietal hits. Nowadays, these instruments have awakened interest as a support to hybrid approaches in translumenal surgery.

APPEARANCE AND DEVELOPMENT OF NOTES

Defined as an acronym for "Natural orifice translumenal endoscopic surgery" (NOTES), the first description of NOTES in animals was made by the Kalloo[7] group in 2004, communicating their successes on a porcine model to which a peritoneoscopy and liver biopsy by the transgastric route had been made. Rao and Reddy[8] performed a peritoneoscopy, hepatic procedures and on genitals with flexible peroral endoscopes with laparoscopic support. In 2006, Reddy and Rao reported the first human appendectomy by the transgastric route: this intervention aroused wide interest in the clinical application of NOTES.

In the following year, several groups described various techniques in animal models that awakened interest in the feasibility and reproducibility of NOTES. Kaloo's group[9,10] reports its satisfactory results performing tubal ligation and transgastric gastrojejunostomies and Thompson's group[11] does the same with their abdominal exploration transgastric experiences and the resection of gynecological organs. In connection with the transgastric cholecystectomy, also in 2005, the groups of Swanstrom and Park[12,13] successfully performed cholecystectomies and transgastric cholecystogastrostomies with flexible endoscopes.

It took 2 years to awaken the interest for clinical application and, during that period of time, the difficulty of safely performing transgastric cholecystectomy was found in experimental animals and access through the vagina was considered and experimented with. The safety of clinical transvaginal NOTES approach was endorsed by its widespread use in the field of gynecology with culdoscopy and with the use of the vaginal route for the extraction of surgical specimens[14-18].

In early March 2007, Zorron's group[19,20] made the first series of transvaginal NOTES cholecystectomies in 4 patients, based on previous experimental studies. Shortly afterwards in the same month, Bessler carried out a successful hybrid transvaginal cholecystectomy with 3 laparoscopic abdominal ports[21]. Marescaux[22], in April 2007, conducted the purest NOTES cholecystectomy in a patient using only an abdominal port through which he introduced a Veress needle for pneumoperitoneum control and a gripper for the vesicular traction. Branco's[23,24] group reported their experience with hybrid cholecystectomy, performing a case with a single abdominal access trocar and then a transvaginal nephrectomy with two 5 mm abdominal trocars. At this time, new applications and a series of cases performed by NOTES take place[25-29].

Transcolonic and transvesical access have been advocated by some researchers as more appropriate for the abdominal approach of supramesocolic structures that are often more difficult to achieve through a transgastric route. Lima's group used combined transgastric and transvesical approaches to increase the feasibility of moderate complexity procedures, such as nephrectomy and cholecystectomy in experimental animals[30]. Feussner[31] published his results on the transcolonic approach in experimental animals, creating potentially safe access to the peritoneal cavity replicable model through access via the sigmoid and upper rectum.

To minimize the access and transparietal support,

new techniques and tools have been developed to perform maneuvres of traction and suspension of the target organ, such as magnets and tissue retractors attached to the parietal peritoneum. Scott's[32] group maintained the traction of the vesicular background with magnets in animals, avoiding the placement of a gateway in the abdominal wall. All these developments are being validated in animal and pilot clinical experiences, with the intention to perform pure NOTES procedures as soon as possible, equipped with the necessary clinical safety.

NOTES: ALLIES AND ENEMIES

Since the clinical application of NOTES began in 2007, we soon realized it would be impossible at that time to perform pure techniques and that laparoscopic support was needed. The development of endoscopes was not progressing quickly and it was necessary to triangulate to maneuvre correctly and safely into the abdomen and tools for hemostasis and sealing of structures that could not be used through the flexible endoscope were also needed. It was necessary to resign from pure NOTES and develop a hybrid NOTES, with more or less support through laparoscopic ports in the abdomen.

Thus, we have seen the techniques using natural orifices as forced allies of NOTES, although rigid material is introduced through them, and to Minilaparoscopy Assisted Natural Orifice Surgery (MANOS) techniques, which use natural orifices for some surgical gestures and the removal of the piece, with support from minilaparoscopy. Both modalities should not be considered as NOTES techniques as long as they do not use the flexible endoscope to perform surgical maneuvres, but their similarity in relationship to the use of natural orifices and the use of minilaparoscopy on the access of the abdomen make this kind of surgery progress together through natural orifices, preferably through the vagina.

Access to the abdomen with rigid instruments from a natural orifice can only be done from a pelvic access. The vagina is the easiest access for its short canal, lack of complications in its access and ease of closing. This kind of rigid NOTES surgery developed by the German group Zornig *et al*[28] has the possibility of using laparoscopic instrumentation and requires no training in handling the flexible endoscope. By contrast, with the MANOS technique, the access through the natural orifices can be done from any entry, not just the vagina, with the possibility of using the endoscope as an instrument that provides light, camera and the ability to help surgery, which is actually performed through minilaparoscopy with parietal abdominal ports. The first description was by Tsin in 2001 under the name of culdolaparoscopy but went unnoticed until the advent of NOTES surgery[33]. Recently, this surgical approach has been applied to the realization of colorectal, splenic and bariatric surgery[34-36].

If these two types of minimally invasive approaches can be considered as allies to NOTES for the contribution to the development of natural orifice surgery, we can also find some developments that may be considered as "enemies" to NOTES. Techniques of single incision and single port involve a major breakthrough for minimally invasive surgery, but they are a step backwards for the development of surgery without scars on the abdomen. It is a conceptual paradigm shift, a radical change in philosophy: from the desire to surgery without scars on the abdomen, to making a single incision but of considerable size and in an area such as the umbilical, with a high risk of incisional hernia[37]. With NOTES, we try to minimize incisions in the abdomen to the point where we can make them disappear. With single-incision surgery we try to hide a minilaparotomy in an area such as the navel. With NOTES, we aim to fight against wound infection and against the generation of hernias and postsurgical adhesions, avoiding trauma to the abdominal wall. With the single-incision surgery, we tend to minimize the importance of these aspects but we do not minimize the risk of their occurrence. Using the flexible endoscope through a transvaginal, transgastric or transumbilical approach is an interesting topic today because in the future, with new endoscopes and flexible endoscopic platforms, we will be able to perform a surgical procedure with them with a single abdominal access. In the meantime, as illustrated in Figure 1, we are evolving from a conventional laparoscopy to other more minimalist approaches.

Many studies are needed so that we can ascertain whether it is better to group trocars into a single incision or keep them separate under a better triangulation in surgery and patient safety. In surgeries where a minilaparotomy for the removal of the piece is not needed, it is difficult to justify the use of this modality; however, in surgeries such as colectomy, splenectomy and other similar surgeries with the extraction of limited size pieces, the use of this access seems very appealing.

INVISIBLE SURGERY IN THE LABORATORY

NOTES surgery has slowed its development for several reasons, among which we can refer to the appearance of single-incision surgery and the fateful economical period of time in which it has been developed. It is a new type of therapeutic procedure with a high dependence on technology that requires a significant investment to develop new platforms, vision systems and instrumentation. The appearance of the single-incision surgery, which manages to reach a wide range of surgical procedures and seems to be more accessible to the entire surgical community with little investment in technology, is going to make us wait for its development and implementation to re-awaken the growing interest in NOTES. Despite all this, transluminal surgery should be further developed. It is necessary that the groups that first began its development carry on with the technique, establishing the needs and specifying the target diseases. Thus, when we are ready to re-address the technological develop-

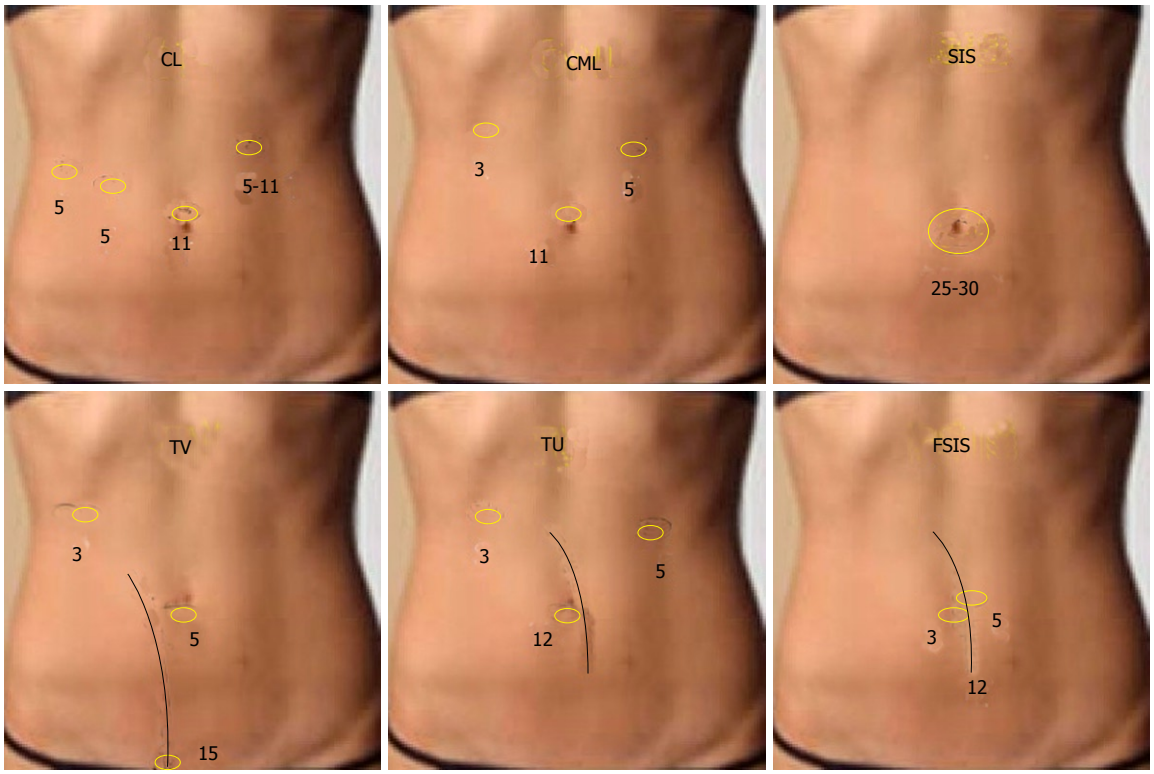

Figure 1 Distribution of the entry-ports by approach to perform cholecystectomy. CL: Conventional laparoscopy. CML: Conventional minilaparoscopy; SIS: Single incision surgery; TV: Flexible or rigid transvaginal endoscopy; TU: Transumbilical flexible endoscopy; FSIS: Flexible single incision surgery.

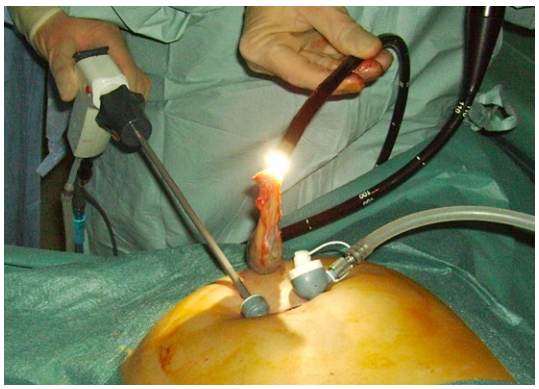

Figure 2 Cholecystectomy by flexible single incision surgery. Umbilical single incision and direct approach with the flexible endoscope without complementary device. Two parallel 5 mm ports are needed to perform a secure procedure.

ment of NOTES, there will be groups who are willing to put the technologies in use which are now sleeping in the labs. While we wait for this new technology, the combination of the flexible endoscopy and minimally invasive access can give us some benefits with a low cost, as can be seen in Figure 2.

Among these new instruments and equipment that are in preclinical research, those which seem to have more interest are the new scopes, the platforms for NOTES and minirobots. The new endoscopes have in common the development of several working channels, up to four, with the intention to give input to instruments in two of them, and at least, to another instrumental working channel to implement elements of coagulation, washing and vacuuming. These new endoscopes can control the pneumoperitoneum and enable joint working tools, getting the necessary triangulation, even in limited space[38,39]. The new miniaturized terminals for bipolar coagulation, tissue sealing, ultrasounds and radiofrequency are shown as very promising elements to facilitate dissection, hemostasis and sealing. Possible future application energies, such as lasers and microwaves, may also have their place through the flexible endoscope.

On the other hand, flexible endoscopes are progressing and the classical concept of a long flexible tube is being substituted by a concept of a translumenal surgery platform which seeks to overcome the difficulties of navigation by stabilizing the transporter of the instruments and allowing a greater skill in movements, endowing a more accurate triangulation and precision[40,41]. These new platforms try to allow the surgeon to make gestures of great similarity to those made in laparoscopic surgery, supported largely by the application of robotics to facilitate accuracy of movements.

Finally, robotics seems to be the technology that will achieve the breakthrough for this type of intracavitary surgery in the not too distant future. The miniature robots are intended to give a step further, putting our vision in intracavitary or intraluminal situation, as well as our tools and the conveyor platform. The simplest ones incorporate the light source and the camera, but the more advanced ones are configured with two arms that even allow surgical maneuvres to be performed[42].

While all these developments come into our hands, it is necessary to promote the combined use of all minimally invasive techniques available to us, as well as team collaboration, which is a fast way of exchanging information and brings the chance to quickly transfer new indications to techniques and specific equipment. The knowledge of the advantages and limitations of each approach allows the development of hybrid techniques where the process cannot be performed without involving both techniques.

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TOPIC HIGHLIGHT

Shigetaka Yoshinaga, MD, PhD, *Series Editor*

Endoscopic ultrasound using ultrasound probes for the diagnosis of early esophageal and gastric cancers

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Abstract

Endoscopic ultrasound (EUS) devices were first designed and manufactured more than 30 years ago, and since then investigators have reported EUS is effective for determining both the staging and the depth of invasion of esophageal and gastric cancers. We review the present status, the methods, and the findings of EUS when used to diagnose and stage early esophageal and gastric cancer. EUS using high-frequency ultrasound probes is more accurate than conventional EUS for the evaluation of the depth of invasion of superficial esophageal carcinoma. The rates of accurate evaluation of the depth of invasion by EUS using high-frequency ultrasound probes were 70%-88% for intramucosal cancer, and 83%-94% for submucosal invasive cancer. But the sensitivity of EUS using high-frequency ultrasound probes for the diagnosis of submucosal invasive cancer was relatively low, making it difficult to confirm minute submucosal invasion. The accuracy of EUS using high-frequency ultrasound probes for early gastric tumor classification can be up to 80% compared with 63% for conventional EUS, although the accuracy of EUS using high-frequency ultrasound probes relatively decreases for those patients with depressed-type lesions, undifferentiated cancer, concomitant ulceration, expanded indications, type 0- Ⅰ lesions, and lesions located in the upper-third of the stomach. A 92% overall accuracy rate was achieved when both the endoscopic appearance and the findings from EUS using high-frequency ultrasound probes were considered together for tumor classification. Although EUS using high-frequency ultrasound probes has limitations, it has a high depth of invasion accuracy and is a useful procedure to distinguish lesions in the esophagus and stomach that are indicated for endoscopic resection.

Key words: Endoscopic ultrasound; High-frequency ultrasound probe; Esophageal cancer; Gastric cancer; Depth diagnosis

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INTRODUCTION

Endoscopic ultrasound (EUS) devices were first designed and manufactured in the early 1980s. Since then, EUS has been adapted not only for pancreatic lesions but also for gastrointestinal and perigastrointestinal lesions, such as gastrointestinal cancers, gastrointestinal stromal tumors,

and abdominal and mediastinal lymphadenopathy. Some investigators have reported EUS is effective for the staging of esophageal and gastric cancers[1,2], and EUS is also useful for determining the depth of invasion of early esophageal and gastric cancers. Ever since Gotoda *et al*[3] described the incidence of lymph node metastasis from early gastric cancer, and with the development of endoscopic submucosal dissection (ESD), many early gastric cancer lesions have been resected endoscopically. In addition, ESD has recently been adapted for excision of esophageal lesions. It is important to accurately estimate the depth of the lesion before endoscopic resection of early esophageal and gastric cancers; a vague estimation of lesion depth may allow residual cancer to remain, leading to recurrences and additional resections.

We review the present status of, the methods used for, and the findings of EUS using high-frequency ultrasound probes for diagnosing and staging early esophageal and gastric cancer.

EUS FOR EARLY ESOPHAGEAL CANCERS

Present status

The depth of early esophageal squamous cell cancer invasion is classified according to six categories that range from only penetrating the epithelium to reaching the proper muscle layer: cancer limited to the epithelium is described as m1; cancer limited to the lamina propria is m2; invasion reaching the muscularis mucosa or invading the muscularis mucosa is m3; invasion of the submucosa less than 200 μm in the endoscopically resected specimen or invasion of the first third of submucosa is sm1; invasion of the submucosa by more than 200 μm in the endoscopically resected specimen or invasion of the second third of submucosa is sm2; and that reaching the proper muscle layer is classed as sm3[4] (Figure 1). The rates of lymph node metastasis in m1 and m2 cancers are estimated at less than 5%, while those of m3 and sm1 cancers are 12%-27%, and those of sm2 and sm3 cancers are 36%-46%[5]. This evidence suggests that invasion depth confined to m1 or m2 regions is a good indication for excision using a procedure such as endoscopic mucosal resection (EMR) or ESD. Therefore, an accurate determination of invasion depth will help distinguish indicated lesions from contra-indicated lesions.

Because EUS using high-frequency ultrasound probes is more accurate than conventional EUS in the evaluation of the depth of invasion of early esophageal carcinoma[6], usually EUS using high-frequency ultrasound probes is performed to evaluate tissue penetration. In previous reports, the accuracies of the depth of invasion measurements by ultrasound probes were 70%-88% for intramucosal cancer, and 83%-94% for submucosal invasive cancer[6-8]. Murata *et al*[4] reported the extent of cancer invasion had been correctly determined in 81% of m1 and m2 lesions, in 60% of m3 and sm1 lesions, and in 87% of sm2 and sm3 lesions. But in another report, the sensitivity for submucosal invasive cancer was only 48%[9], and overall accuracy, sensitivity, and specificity to

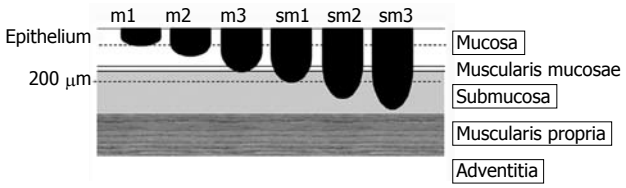

Figure 1 Scheme of the depth of esophageal cancer invasion.

differentiate submucosal invasive cancers from intramucosal cancers were 74%, 62%, and 77%, respectively[10]. Especially, May *et al*[9] reported the diagnostic accuracy was not yet satisfactory with submucosal invasive cancers located at the esophagogastric junction (EGJ) or with infiltration of the first third of the submucosa. In addition, it is difficult to distinguish between cancer invasion and inflammatory cell infiltration[4]. Thus, although EUS can distinguish between definite intramucosal cancers and definite submucosal invasive cancers, it is relatively difficult to confirm minute submucosal invasion even when using high-frequency probes.

Although water introduced normally into the esophagus can provide acoustic coupling for EUS, it is difficult to submerge the target lesion because the water flows off easily. To solve this problem, some investigators developed EUS devices utilizing either a water-filled balloon method[11], a device for continuous irrigation of water[12], or a jelly-filled method[13]. However, the balloon interferes with the diagnosis of m1 and m2 cancer, so the water or the jelly-filled methods may be preferred[4,13,14]. In our institute, we use an endoscope with a water-jet system to provide irrigation.

EUS methods in our institute

Our EUS procedure is performed using a 20 MHz ultrasound probe (UM-3R; Olympus Optical Co, Ltd, Tokyo, Japan) with an endoscopic ultrasound system (EU-M2000; Olympus) through a forward-viewing endoscope with a water-jet system (GIF-Q260J; Olympus). Deaerated water is boiled at least one day before the procedure and then allowed to rest to remove any bubbles. This preparation is necessary to achieve accurate data from the EUS procedure (Figure 2A and B).

For premedication, scopolamine butylbromide as an antispasmodic and midazolam as a sedative, and, occasionally, pethidine hydrochloride as an analgesic, are administered to the patients. After the patients have received the premedication, their blood pressure, heart rate, and arterial oxygen saturations are monitored until an hour after the procedure is finished.

With patients lying in a left lateral decubitus position, we insert an endoscope into the esophagus and attempt to visualize a lesion; if one is discovered, mucus and saliva on the lesion are washed away gently (Figure 3A). An ultrasound probe is inserted through an instrument channel and we begin irrigating with deaerated water through a water jet channel operated by an assistant, while we watch the lesion directly. After sufficient deaerated water is present to act as an acoustic coupling medium, ultra-

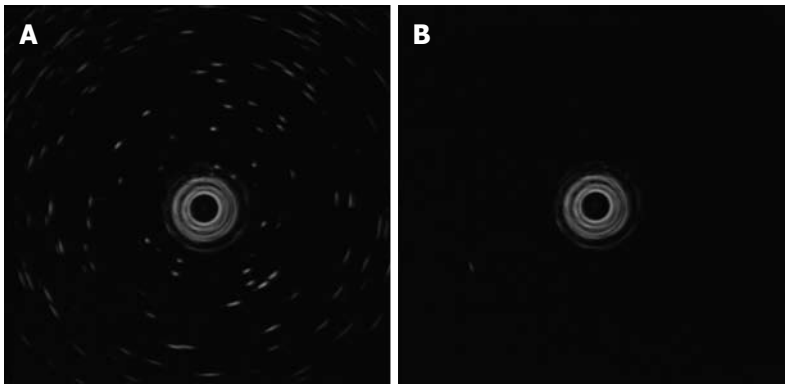

Figure 2 Differences in endoscopic ultrasound features with quality of water used for irrigation. A: Water from a faucet ; B: Deaerated water.

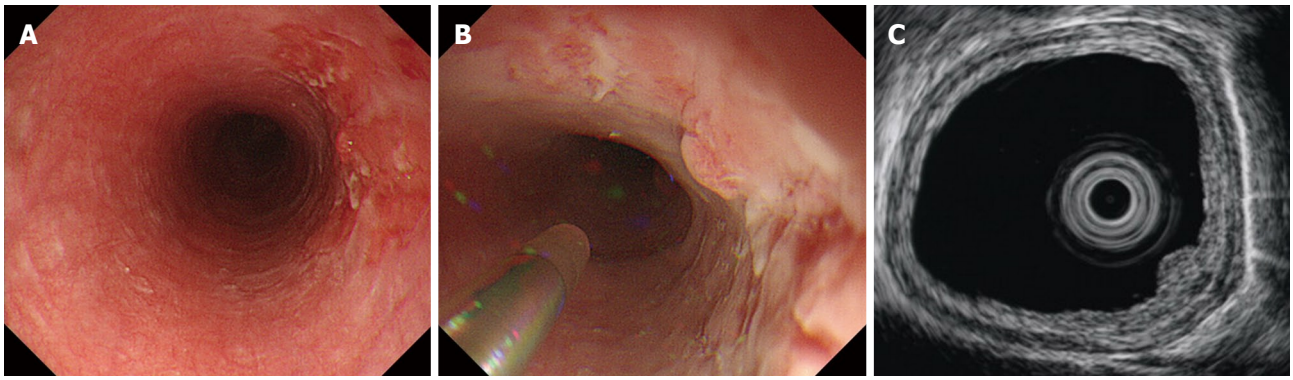

Figure 3 Endoscopic ultrasound procedure for early esophageal cancer as performed at the National Cancer Center Hospital. A: Endoscopic features after washing mucus and saliva from the lesion; B: Endoscopic features after region is filled with deaerated water. Endoscopic ultrasound (EUS) can be performed under direct vision of the lesion; C: EUS features.

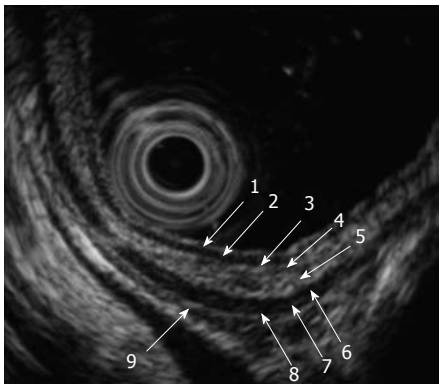

Figure 4 Endoscopic ultrasound features of normal esophageal wall. Each numbered circle, 1-9, with a white arrow, indicates the corresponding numbered tissue layer, first through ninth.

sound scanning is begun (Figure 3B and C). Technically, it is difficult to scan lesions which are located near EGJ precisely because the lower esophagus is sometimes spastic or not distended.

EUS findings for early esophageal cancers

When we use high-frequency ultrasound probes, the esophageal wall is delineated as nine alternating high- and low-echo layers[4]. The first to the fourth layers represent the mucosa, with the first and second layers corresponding to the epithelium, the third layer to the lamina propria, and the fourth layer to the muscularis mucosa. The fifth layer is the submucosa. The sixth to eighth layers are the proper muscle layers, with the sixth layer corresponding to the circular muscle, the seventh to the connective tissue and interface, and the eighth layer to the longitudinal muscle. The ninth layer is the adventitia (Figure 4).

Cancers are visualized as hypoechoic lesions, and it should be recognized which layers are destroyed and which layers are normal. An m1 cancer is located in the first and second layers[4], and sometimes it is difficult to recognize the lesion (Figure 5A-D). An m2 cancer invades the third layer, but the fourth layer under the lesion is preserved (Figure 6A-D). Cancers with m3 to sm1 invasion penetrate the fourth layer, but the fifth layer is intact[4] (Figure 7A-D). In some cases of sm1 cancer, the fifth layer under the lesions appears slightly irregular (Figure 8A-D). An sm2 cancer invades the fifth layer, but there is a hyperechoic layer between the cancer and the sixth layer[4] (Figure 9A-D).

EUS FOR EARLY GASTRIC CANCERS

Present status

According to the report by Gotoda *et al*[3], the expanded indications of endoscopic resection for gastric cancer are defined as follows: (1) differentiated type, no lymphatic or venous invasion, intramucosal cancer without ulceration, regardless of tumor size; (2) intramucosal cancer with ulceration, less than 3 cm diameter; (3) minute submucosal cancer that invades less than 500 μm in the submucosa,

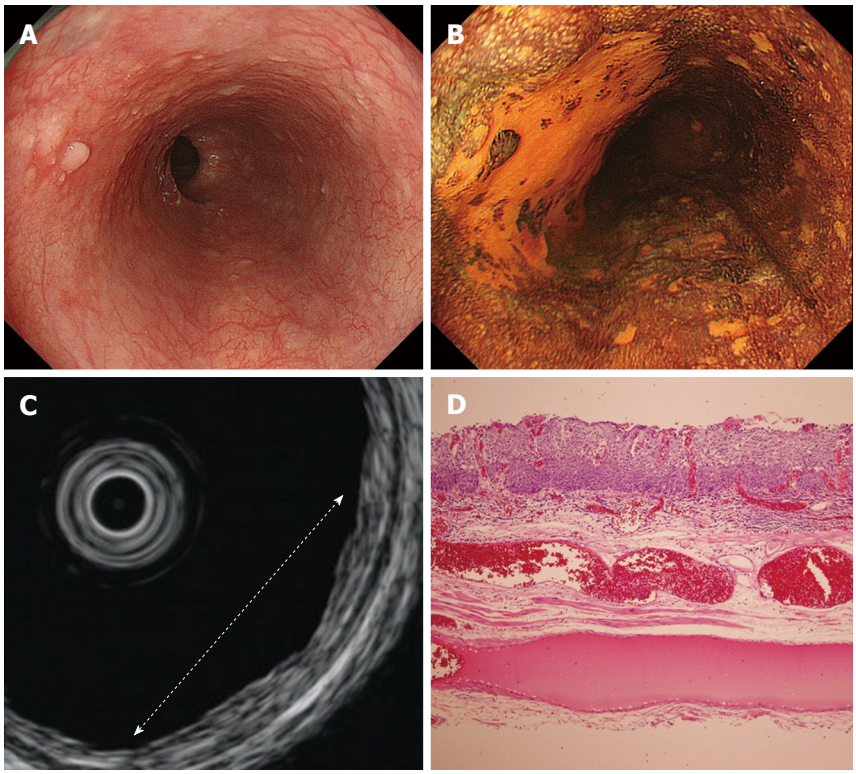

Figure 5 Findings for an m1 cancer of the esophagus. A: Endoscopic features. A reddish depressed lesion was located on the anterior and left wall of the middle esophagus; B: Endoscopic features after iodine dye. Biopsy specimens showed squamous cell carcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed an irregularity of the first layer and a slight thickness of the second layer; D: Pathological findings. The tumor was confined to the epithelium. (Hematoxylin and eosin stain, × 40).

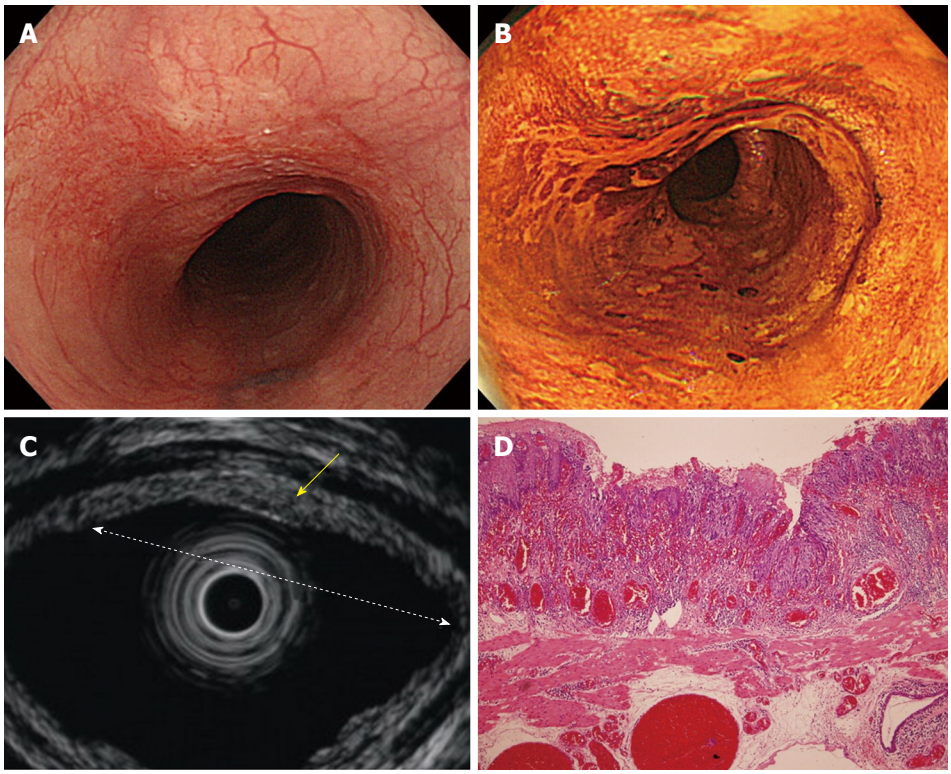

Figure 6 Findings for an m2 cancer of the esophagus. A: Endoscopic features. A reddish flat lesion was located on the anterior wall of the middle esophagus; B: Endoscopic features after iodine dye. Biopsy specimens showed squamous cell carcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed a thickness in the second layer and a disappearance of the third layer. The yellow line with an arrow indicates the intact fourth layer; D: Pathological findings. The tumor was confined to the lamina propria. (Hematoxylin and eosin stain, × 100).

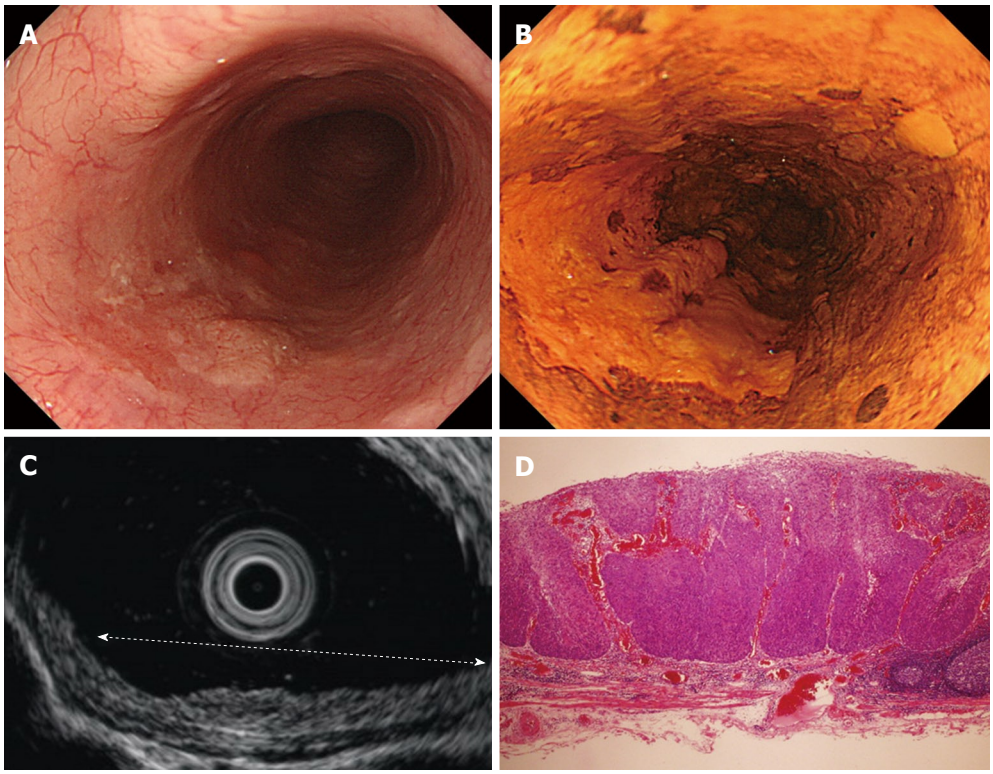

Figure 7 Findings for an m3 cancer of the esophagus. A: Endoscopic features. A reddish flat and partially elevated lesion was located on the posterior wall of the middle esophagus; B: Endoscopic features after iodine dye. Biopsy specimens showed squamous cell carcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed a thickness of the second layer and a disappearance of the third and fourth layer. The fifth layer seemed to be intact; D: Pathological findings. The tumor was reaching and partially invading the muscularis mucosae. (Hematoxylin and eosin stain, × 40).

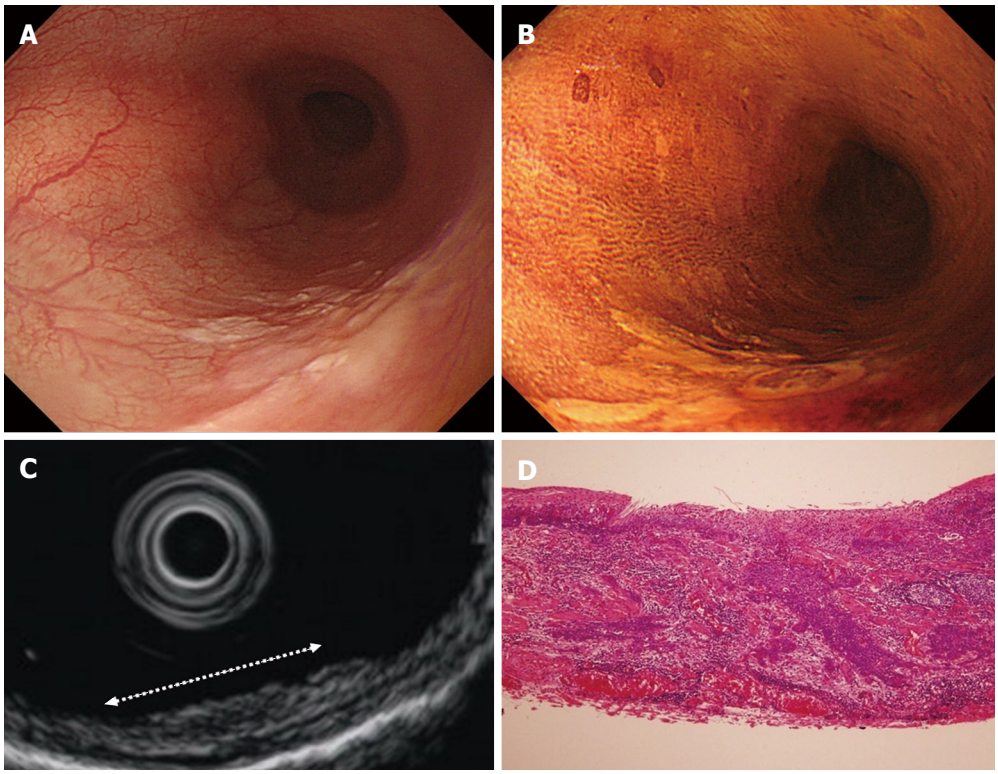

Figure 8 Findings for an sm1 cancer of the esophagus. A: Endoscopic features. A depressed, white, flat lesion was located on the posterior wall of the middle esophagus; B: Endoscopic features after iodine dye. Biopsy specimens showed squamous cell carcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed a thickness of the second layer and a disappearance of the third and fourth layer. The fifth layer seemed to be slightly irregular; D: The tumor was invading the submucosal layer to about 170 μm in depth. (Hematoxylin and eosin stain, × 40).

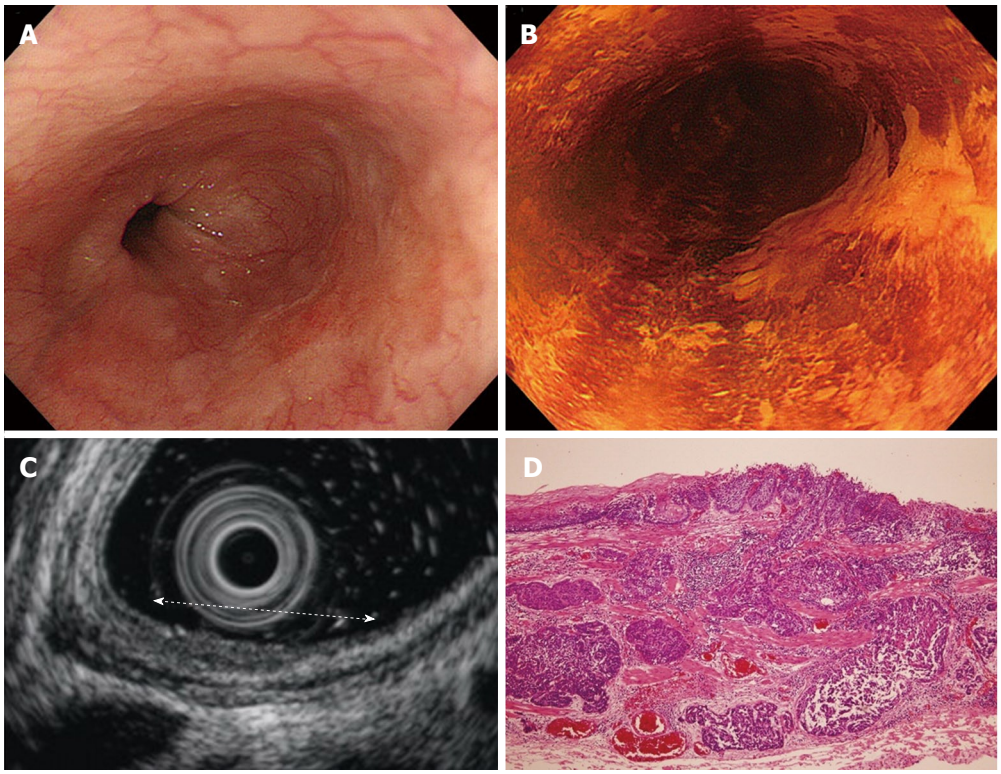

Figure 9 Findings for an sm2 cancer of the esophagus. A: Endoscopic features. A depressed lesion was located on the posterior and right wall of the middle esophagus; B: Endoscopic features after iodine dye. Biopsy specimens showed squamous cell carcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed a thickness of the second layer and a disappearance of the third and fourth layer. The fifth layer had become thin, but the sixth layer was intact; D: Pathological findings. The tumor was invading the submucosal layer to a 320 μm depth. (Hematoxylin and eosin stain, × 40).

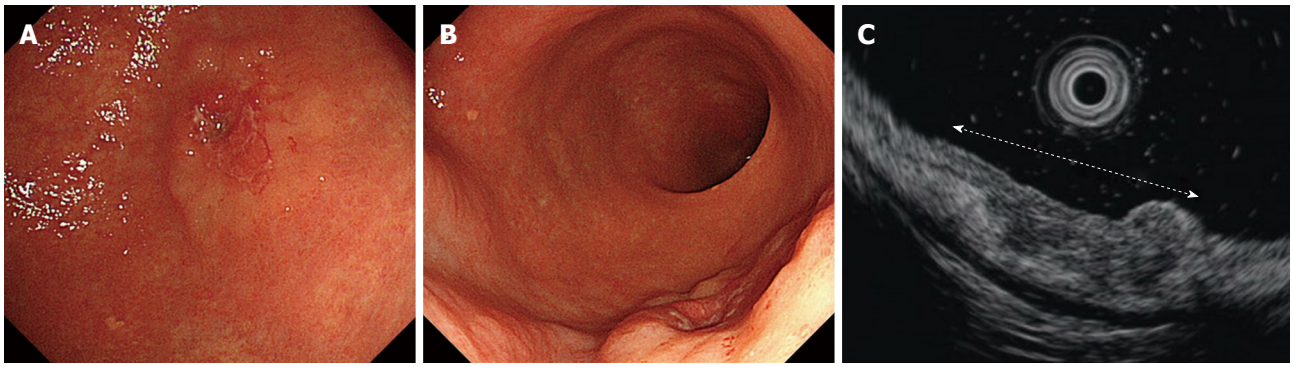

Figure 10 Endoscopic ultrasound procedure as performed at the National Cancer Center Hospital when it is difficult to approach lesions horizontally. A: Elevated lesion with central depression was located on the greater curvature of the angle; B: The lesion could be approached horizontally when using a multi-bending endoscope; C: Endoscopic ultrasound features after region is filled with deaerated water.

less than 3 cm diameter; and (4) undifferentiated type, no lymphatic or venous invasion, intramucosal cancer without ulceration, less than 2 cm diameter. Therefore, we should distinguish intramucosal (m) cancer, minute submucosal invasive (sm1) cancer, and massive submucosal invasive (sm2) cancer.

The accuracies of EUS using high-frequency ultrasound probes for the staging of early gastric cancer have been described as up to 80% compared with 63% for conventional EUS[15]. Rodriguez *et al*[16] mentioned that many endosonographers now feel that catheter-based miniprobes scanning at 20 MHz may be better suited to staging early gastric cancers. In previous reports, the overall accuracies of the depth of invasion by the ultrasound probes were 65%-86%[17-20]. In those reports, the accuracy of EUS relatively decreased for those patients with lesions of depressed type, undifferentiated cancer[18,19], concomitant ulceration, the expanded indications that we described[19], type 0-I lesions, and lesions located in the upper-third of the stomach[20]. Also, Akahoshi *et al*[18] mentioned that the accuracy decreased as tumor size increased. In addition, over staging of early gastric cancers with the 20 MHz probe occurs in 19%-24% of patients due to peritumoral fibrosis mimicking deeper invasion[16,17,21]. But when both the endoscopic appearance and EUS findings were applied together for tumor classifica-

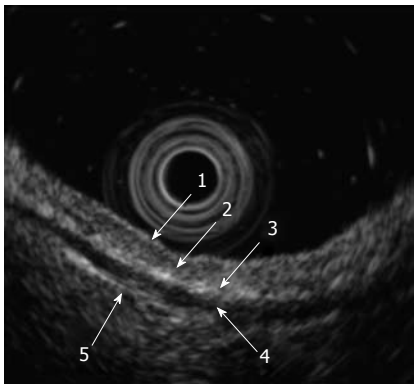

Figure 11 Endoscopic ultrasound features of normal gastric wall. Each numbered circle, 1-5, with a white arrow, indicates the corresponding numbered tissue layer, first through fifth.

tion, a 92% overall accuracy rate was achieved[17]. Though Mouri *et al*[22] reported both high-frequency ultrasound probes and conventional EUS are useful for accurately determining the depth of invasion of gastric cancer without ulcerous change, they did not distinguish between intramucosal cancers and minute submucosal invasive cancers in terms of the expanded indication of endoscopic resection, and they also excluded the lesions that EUS could not sufficiently evaluate. In other words, it is still difficult to distinguish those cancers, especially with ulcerous change, and EUS cannot evaluate all gastric lesions.

EUS methods in our institute

Our preparations and patient premedications are the same for both gastric and esophageal EUS procedures. Usually, we use a conventional endoscope that can be bent more than 180 degrees, both because we don't need to use a water jet system for gastric EUS and because sometimes we need to scan at the retroflex position.

After washing the lesion and removing water collected in the stomach, we start irrigating with deaerated water introduced through an instrument channel. After the area to be imaged is filled with deaerated water, an ultrasound probe is inserted through an instrument channel and ultrasound scanning is begun. When it is difficult to approach lesions horizontally (Figure 10A) it is sometimes impossible to scan. In such cases we use a multi-bending endoscope (GIF-2TQ260M; Olympus) to approach lesions horizontally (Figure 10B and C). Technically, it is sometimes difficult to scan lesions which are located in the angle and the antrum because lesions are located on the curve or not submerged under water.

EUS findings for early gastric cancer

When we use high-frequency ultrasound probes, the normal gastric wall is visualized as the mucosa (combination of the first hyperechoic and second hypoechoic layers) and the submucosa (the third hyperechoic layer). The muscularis propria is visualized as the fourth hypoechoic layer, and the fifth hyperechoic layer is the serosa including the subserosa (Figure 11)[17]. According to the report by Yanai *et al*[23] the fine hypoechoic layer between the second and third layers is considered to correspond to the muscularis mucosae.

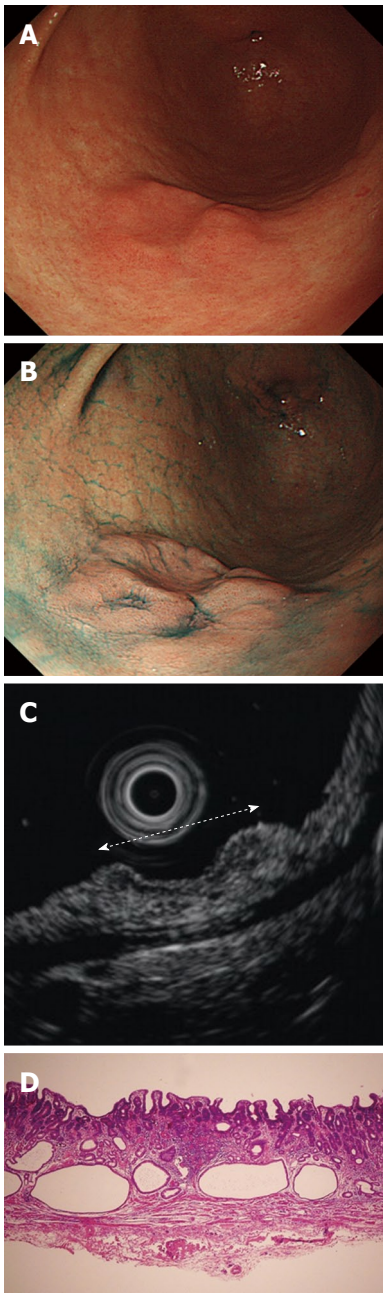

Figure 12 Findings for an m cancer of the stomach. A: Endoscopic features. A depressed lesion with surrounding elevation was located on the greater curvature of the antrum; B: Endoscopic figure after indigo carmine dye. Biopsy specimens showed adenocarcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed an irregularity of the first layer and a slight thickness of the second layer; D: Pathological findings. The tumor was confined to the lamina propria. (Hematoxylin and eosin stain, × 40).

The EUS images were interpreted with regard to tumor invasion according to the five layer architecture of the gastric wall, and lesions were classified as m cancers (Figure 12A-D) and submucosal invasive (sm) cancers[17] (Figure 13A-D). Although the fifth layer under the lesions seems to be slightly irregular in some cases of sm1 cancer (Figure 14A-D), it is difficult to distinguish m and sm1 definitively.

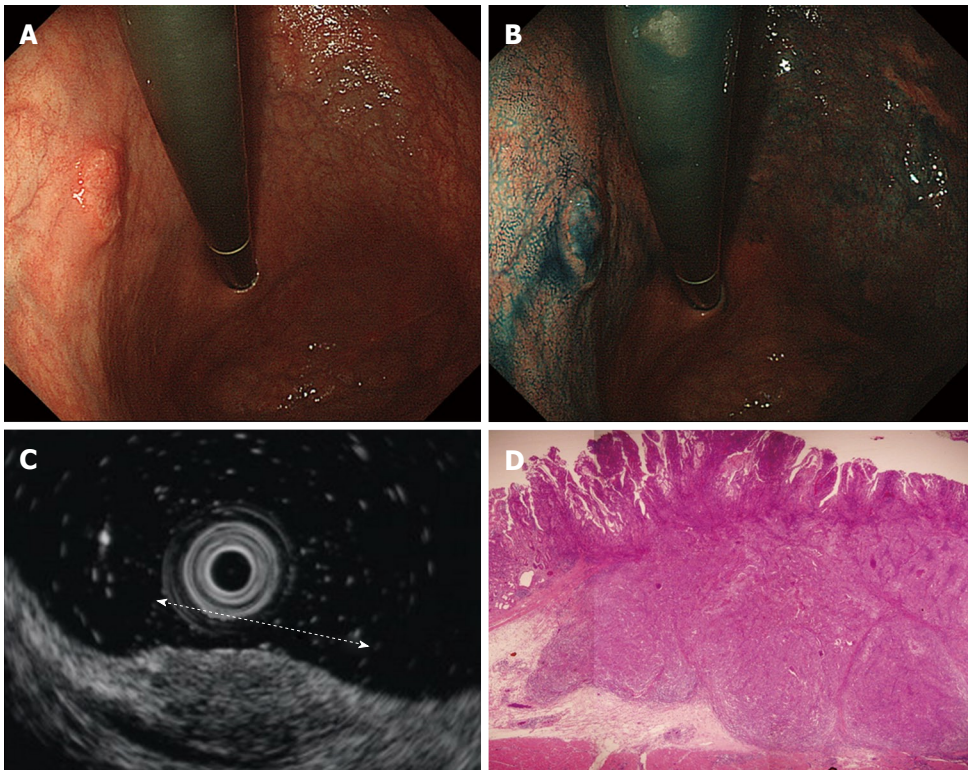

Figure 13 Findings for an sm2 cancer of the stomach. A: Endoscopic features. An elevated lesion was located on the posterior wall of the upper gastric body; B: Endoscopic features after indigo carmine dye. Biopsy specimens showed adenocarcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed a thickness of the second layer and a thin third layer, but the fourth layer was intact; D: Pathological findings. The tumor was invading the submucosa massively. (Hematoxylin and eosin stain, × 12.5).

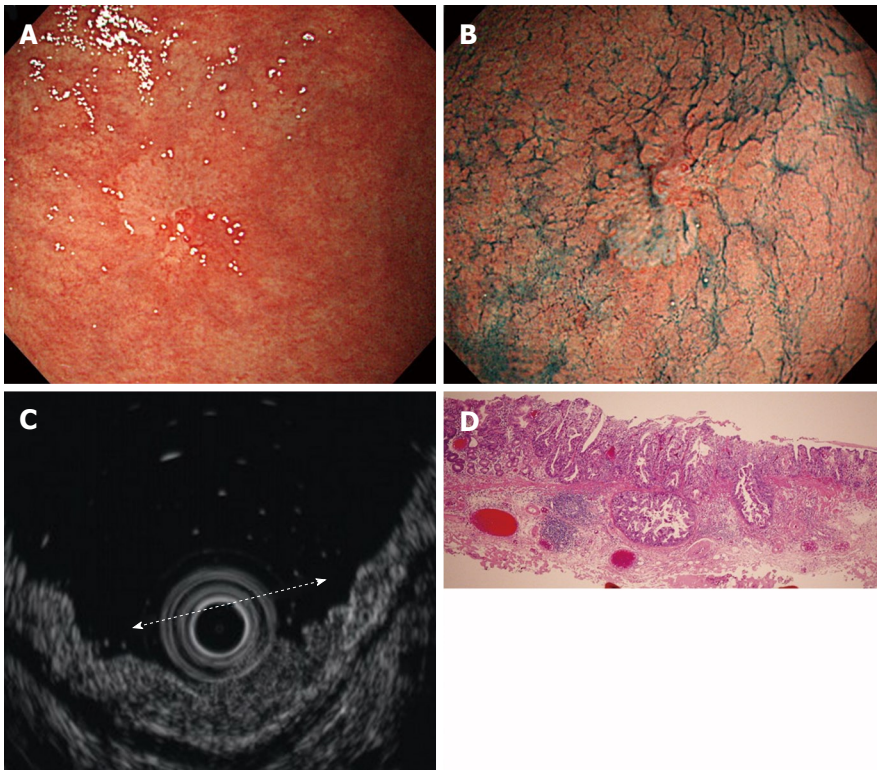

Figure 14 Findings for an sm1 cancer of the stomach. A: Endoscopic features. A white, flat lesion with central elevation was located on the greater curvature of the angle; B: Endoscopic features after indigo carmine dye. Biopsy specimens showed adenocarcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed a thickness of the second layer and a slightly irregular third layer; D: Pathological findings. The tumor was invading the submucosal layer to a 400 μm depth. (Hematoxylin and eosin stain, × 40).

COMPLICATIONS OF EUS

Fortunately, no severe complications of EUS have been reported so far, but aspiration of water occurs occasionally. There is a larger risk for this when patients have a hiatal hernia, as water collected in the stomach runs back easily. Therefore, conscious sedation, rather than deep sedation, is more suitable for EUS. If possible, a balloon should be fixed oral to the tips of an endoscope to prevent water reflex[4] for esophageal lesion procedures.

CONCLUSION

We reviewed the present status of, the methods used for, and the findings of, EUS using high-frequency ultrasound probes to diagnose and stage early esophageal and gastric cancer. Although EUS using high-frequency ultrasound probes still has some limitations, such as low accuracy for minute submucosal invasion cancers and lesions with ulcerous change, it still has good accuracy for determining the depth of invasion of early esophageal and gastric cancers. Because determining the depth of malignant invasion is essential to distinguish lesions indicated for endoscopic resection, EUS is a useful clinical procedure. When both the endoscopic and EUS diagnoses are considered, clinicians can achieve a high accuracy of staging of early esophageal and gastric cancers.

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OBSERVATION

Informed consent for digestive endoscopy

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Abstract

Informed consent is necessary in good clinical practice. It is based on the patient´s ability to understand the information about the proposed procedure, the potential consequences and complications, and alternative options. The information is written in understandable language and is fortified by verbal discussion between physician and patient. The aim is to explain the problem, answer all questions and to ensure that the patient understands the problems and is able to make a decision. The theory is clear but what happens in daily practice?

Key words: Informed consent; Endoscopy; Written consent; Uninformed consent

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INTRODUCTION

There is a general consensus that every patient coming for digestive endoscopy has the right and should be informed in an adequate, appropriate and understandable way about the procedure. This information should be given in a timely fashion before the endoscopy and should provide a description of the test comprehensibly, explain the reason for investigation, the alternatives, possible risks and benefits, and main implications. It is mandatory to have time and the opportunity to ask additional questions. The decision to undergo endoscopy should not be made under duress and confirmed by the patient's signature on a written form of informed consent. Thus, everything is clear. However, daily routine practice is a little bit more complicated.

PATIENTS AND METHODS

According to a survey of the European Society of Gastrointestinal Endoscopy (ESGE) in 2002[1], the procedure for obtaining informed consent for digestive endoscopy varies considerably. A structured questionnaire regarding the quality of informed consent was sent to particular endoscopic societies that are members of the ESGE. The response rate was 59% (26/44). The required information is given prior to written consent in only 23% (6/26) of the countries. Information about the procedure is given to the patients in 96% of the responding countries and in only 77% is there sufficient time for patients to ask questions about the nature of the test. In 15% (4/26) of the countries, neither diagnostic nor therapeutic alternatives to endoscopy or the potential complication rate are discussed[1]. Other published data available is rather controversial. Several studies had different experiences. For instance, in one survey, 92% of patients were properly informed[2], while according to others, 51% felt dissatisfied because they would have

wanted more information (before diagnostic endoscopy) and 25% to 76% had not been adequately informed about the potential risks (of diagnostic endoscopy or endoscopic retrograde cholangiopancreatography) and alternative methods (to percutaneous endoscopic gastrostomy)[3-5]. In a Veterans Administration study[6], all patients signed the consent form before sigmoidoscopy but only 14% of patients actually read all of it (most thought that they had enough information to proceed with the endoscopy). Most patients (93%) were given the opportunity to ask questions but only 22% actually did so[6]. Some gastroenterologists are afraid that patients undergoing open access endoscopy are less likely to be properly informed about their endoscopic procedure than the group of patients referred from specialized clinics[7]. Others propose to send information booklets or leaflets on endoscopy procedures in advance by post[8] or provide patients with information by means of computer-based visualization[9]. Despite all non-homogenous data, it is quite clear that informed consent is only one of the items of information needed by patients before digestive endoscopy.

However, some demands are difficult to meet. Mayberry[10] studied levels of information required by patients (516 persons contacted) and solicitors specializing in clinical negligence (79 subjects addressed) before gastroscopy and flexible sigmoidoscopy. Of the solicitors, 86% felt that patients needed to be informed about the procedure on at least two occasions and favored booklets and videos. Both 75% of solicitors and 44% of patients thought that informed consent for endoscopy should be obtained 2 wk before the test. Forty-eight percent of solicitors and 38% of patients felt that patients should be told of very uncommon risks (16% of solicitors even expected information about risks of 1 in 1 000 000)[10]. According to the British Society of Gastroenterology Guidelines for Informed Consent[3], the patient should be fully informed by the endoscopist ideally at least 24 h before the procedure; however, for busy units these are impossible standards[3].

A significant number of patients (41%) signing informed consent were worried by the explanation of the risks (before laparoscopy)[11].

Another study was carried out at the Inverclyde Royal Hospital, Greenock, Scotland. Demosthenous *et al*[12] used validated tests of memory on 59 patients undergoing lower limb arthroplasty to assess how well they learned and recalled information about their planned procedure. Neuropsychological tests were administered to measure the patient's ability to receive, store and recall information delivered verbally. All patients showed an ability to learn new material; however, younger age and higher educational achievement correlated with better performance (patients were excluded if they had any condition impairing memory or communication: dementia, cerebrovascular disease, epilepsy, head injury, dysphasia or aphasia). These results have serious implications for orthopedic surgeons discussing planned procedures. They identified groups of patients who may require enhanced methods of communicating the objectives, risks and alternatives to surgery.

One third of patients were distressed or surprised to be given oral or written information in a French study, obtaining informed consent for digestive endoscopy was distressing for 20% of those subjects[13]. In another French study[14], 10% of patients considered that the written consent for gastrointestinal endoscopy altered their trust in their endoscopist. Discussions of risk must especially be made in a friendly manner[15] and should not frighten the patient or even discourage him/her from undergoing the endoscopy.

Informed consent has been set within the framework of medical ethics. Whenever possible, patients should remain responsible for themselves. Where a choice of investigation/treatment might be reasonably offered, the physician may always advise the patient of his/her recommendation (together with reasons for such a suggestion). Clinicians must respect the need to maintain the autonomy and self-determination of patients[16]. Nevertheless, the question of protecting physicians from malpractice claims is a major aspect of the guidelines for informed consent of the British Society of Gastroenterology[16] and the American Society for Gastrointestinal Endoscopy[17].

It is questionable whether all endoscopy units working within particular societies of gastrointestinal endoscopy should use identical protocols of informed consent. For instance, the British Society of Gastroenterology[16] recommends that each unit should develop its own code of practice suitable to its mode of operation. However, some elements are universal and should always be included. The clinician proposing an endoscopic procedure should explain the reasons for the test and describe its essential elements[16,18]. Prior to the endoscopy, patients should be provided with written information in a timely fashion and in a form understandable to the patient[12,15].

The written information describes the principles of investigation and the reasons it is performed. It must list diagnostic/therapeutic alternatives to the test and explain possible major complications (in terms that the patient will understand). It is important to mention in writing that findings within endoscopy and/or possible complications may extend the investigation and/or change the treatment. It is mandatory to inform the patient about who has overall responsibility for the procedure and reassure him/her that the endoscopist and all the staff will do their best for the patient's benefit. A special part of informed consent should provide information about conscious sedation and its consequences (the patient will not be able to drive a vehicle, operate apparatus requiring full vigilance and must refrain from alcohol consumption for 24 h after the test). The patient must have an opportunity to ask additional questions. He/she must be also advised whom to contact in case of any complaint or complication after his/her discharge from the unit (including telephone number for consultation). A psychological approach to the patient is essential, in-

cluding further clarification, reassurance and calming of any possible fears. Naturally, the form (appended with date, time and place) identifies not only the patient but also the unit and the responsible physician. After a full explanation and comprehension, the informed consent is signed by the patient and responsible physician. The form for informed consent should be prepared in duplicate, one for patient and one for medical records.

There are some special situations that should also be mentioned. The first one is "uninformed consent". Some patients agree with endoscopy but state that they do not wish to receive any information about the procedure and this should be respected. Ethically, information cannot be forced on them but their uninformed consent would still be valid if they are offered detailed information and if they understand that such information is available for them[18]. Parents (or guardians) will give (and sign) informed consent on behalf of their children and guardians (or first-degree relatives) on behalf of mentally disabled patients[18]. Special endoscopic procedures (insertion of esophageal or biliary stents and percutaneous endoscopic gastrostomy placement) should also be discussed in detail, including matters of long-term management and potential problems. Some of these patients are in a serious condition and their capacity to give consent may vary due to cerebral dysfunction. Consent may be possible orally or by gesture alone but since gastrostomy placement is an invasive procedure, a reasonable degree of certainty that the patient has consented plus discussion with relatives is needed in every case[16]. Since informed consent is a process and not a single event, post procedural follow-up of patients is obligatory[18]. In cases of an emergency (when the situation is life threatening or it is necessary to relieve severe pain and suffering), no consent is necessary, the endoscopist takes full responsibility and acts in the patient's best interest[16,18]. The understanding of the risks of endoscopy is insufficient, especially in the cases of older, poorly educated patients and outpatients[19]. It is also very important to respect a language barrier[20].

Technological progress has recently brought a lot of new endoscopic methods and devices. The 21th century especially has enriched gastroenterology with new great possibilities: balloon or deep enteroscopy, capsule enteroscopy, confocal laser endomicroscopy, biodegradable stents *etc*. Some of new endoscopic methods are still under evaluation and their yield and safety aspects must be further determined. These facts must be taken into account in the informed consent.

Lastly but not least, it is necessary to emphasize that the patient has a right to withdraw his/her previous consent at any time before or during the endoscopy. If the patient is under conscious sedation when requesting to end the procedure, the physician should make a judgement based on the best interests of the patient[18]. The Latin saying "salus aegroti suprema lex" (the patient's benefit is the highest law) must not be forgotten at any time.

CONCLUSION

Informed consent is only one of the items of information needed by patients before digestive endoscopy. It is mandatory to give the patient time and the opportunity to ask additional questions. The clinician proposing an endoscopic procedure should explain the reasons for the test and describe its essential elements. Prior to the endoscopy, patients should be provided with written information in a timely fashion and in a form understandable to the patient. It is necessary to emphasize that the patient has a right to withdraw his/her previous consent at any time before or during the endoscopy.

Movement away from "informed consent" towards an "informed decision" would be the target we should reach in the near future.

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OBSERVATION

Supportive techniques and devices for endoscopic submucosal dissection of gastric cancer

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Abstract

The indications for endoscopic treatment have expanded in recent years, and relatively intestinal-type mucosal stomach carcinomas with a low potential for metastasis are now often resected *en bloc* by endoscopic submucosal dissection (ESD), even if they measure over 20 mm in size. However, ESD requires complex maneuvers, which entails a long operation time, and is often accompanied by complications such as bleeding and perforation. Many technical developments have been implemented to overcome these complications. The scope, cutting device, hemostasis device, and other supportive devices have been improved. However, even with these innovations, ESD remains a potentially complex procedure. One of the major difficulties is poor visualization of the submucosal layer resulting from the poor countertraction afforded during submucosal dissection. Recently, countertraction devices have been developed. In this paper, we introduce countertraction techniques and devices mainly for gastric cancer.

INTRODUCTION

The incidence of gastric cancer is high in East Asia, Eastern Europe and South America. In Japan, 50 000 people a year die from gastric cancer, so countering gastric cancer is an important mission. Early detection and early treatment are regarded as the most important factors in the treatment strategy. In patients with early gastric cancer (mucosal stomach cancer), endoscopic submucosal dissection (ESD) enables *en-bloc* dissection of larger lesions than that by endoscopic mucosal resection (EMR)[1-3]. *En-bloc* resection allows more accurate pathological diagnosis and reduces the risk of recurrence[3-6].

However, ESD requires complex technical maneuvers and a long operation time. Moreover, complications such as bleeding and perforation occur more frequently with ESD than with EMR[2,3,7]. To overcome these complications, many supportive techniques and devices have been developed.

We classify supportive techniques and devices under the following 3 categories: (1) improvements to the

scope [magnifying endoscopy[8-10], the narrow band imaging system[11-13] and the flexible spectral imaging color (FICE) system[14], scopes with a built-in forced irrigation channel[15], and so on]; (2) cutting and hemostasis devices (high frequency generator[16], various knives[17-19], various hemostasis forceps[20], various hemostasis clips and so on); and (3) other supportive devices (local injection agents[21]) and CO_2 insufflations to the alimentary tract[22]). Even with these innovations in place, ESD is still not easy. One of the major difficulties is poor visualization of the submucosal layer resulting from the poor countertraction afforded during submucosal dissection, therefore countertraction devices have been developed in recent years[23-39]. These countertraction devices could be placed in the 4th category in addition to the three outlined above. The focus of this article will be countertraction devices (Table 1).

Table 1 Classification of countertraction devices and methods

Double endoscope methods	Authors	Year
Double endoscopic intralumenal operation (DEILO)	Kuwano *et al*[23]	2004
Thin endoscope-assisted ESD	Uraoka *et al*[25]	2010
Transnasal endoscope-assisted ESD	Ahn *et al*[24]	2010
Countertraction tool attached to the endoscope		
Small-caliber-tip transparent hood	Yamamoto[26]	2003
Double-channel therapeutic endoscope (the "R-scope")	Yonezawa *et al*[29]	2006
Multipurpose treatment hood (TxHood)	Kawano *et al*[28]	2008
Angler fish-type countertraction system	Sakurazawa *et al*[30]	2009
Sheath-assisted countertraction ESD	Hijikata *et al*[27]	2010
Countertraction tool independent of the endoscope		
Percutaneous traction-assisted EMR	Kondo *et al*[31]	2004
Magnetic anchor system	Kobayashi *et al*[33]	2004
External grasping type of forceps	Imaeda *et al*[34]	2006
Internal traction using a nylon loop	Chen *et al*[36]	2007
Percutaneously-assisted endoscopic surgery using a new PEG-minitrocar	von Delius *et al*[32]	2008
Peroral traction-assisted ESD	Jeon *et al*[39]	2009
Spring-assisted ESD	Sakurazawa *et al*[40]	2009
The pulley method ESD	Li *et al*[38]	2010
Medical ring system	Matsumoto *et al*[35]	2011
Clip-band technique	Parra-Blanco *et al*[36]	2011

ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection.

SUPPORTIVE TECHNIQUES AND DEVICES FOR ESD

Improvements to the scope

Zoom endoscopy magnifies the surface structure of tumors and allows the operator to detect the precise border of the tumor[8-10]. The narrow band imaging system (NBI) selects a spectrum of the emitted illumination to enhance the structure of the blood vessels and the tumor border. By using these systems, a more accurate diagnosis is obtained to avoid unnecessary resection of the lesion to reduce the risk of bleeding and perforation[11-13]. The FICE system is different from the NBI system in that it allows selection of the limited spectrum of the light being reflected from the lesion to enhance detection of the border between the tumor and normal mucosa[14]. The water-jet scope can immediately wash away bleeding during an ESD procedure. With this facility, bleeding points can be precisely identified, and we can stop bleeding more easily[15].

Cutting and hemostasis devices

The new high frequency generator calculates the electrical resistance of the tissue instantly, and changes the current flowing though the electric knife depending on the electrical resistance of the tissue to enhance coagulation thus decreasing bleeding from the area of incision[16].

Various knives (IT knife, Hook knife, and Flex knife) have been developed[17-19], in addition to various hemostasis forceps and hemostasis clips[20]. These innovations now allow us to use the most appropriate knife, hemostasis forceps and hemostasis clips in each scene of ESD.

Other supportive devices and techniques

As a substitute for saline which is used conventionally, a new local injection agent was developed based on hyaluronic acid. Following the use of hyaluronic acid, the mucosal elevation time improved markedly[21]. Because mucosal elevation was stable for a long time, the risk of perforation was reduced. In recent years, CO_2 insufflation has been used for ESD. Because, CO_2 is more quickly absorbed in water than air, even in the event of a perforation-related pneumoperitoneum occurring, the CO_2 is absorbed immediately[22]. This helps to prevent perforation-related pneumoperitoneum compartment syndrome.

Countertraction devices

Various countertraction devices have been developed. We have classified these devices under the following three types: double endoscope methods, countertraction tool attached to the endoscope, countertraction tool independent of the endoscope.

Double endoscope method: This method involves the use of two scopes as two endoscopists are sometimes required, one scope lifts the lesion and the other resects it. The merit of this technique is that the direction and strength of countertraction can be obtained by manipulating the lifting scope. The demerit is that their movements are slightly affected by friction between the two scopes. Kuwano *et al*[23] reported a double endoscopic intralumenal operation. This novel technique is characterized by the use of two endoscopes. One scope lifts the lesion in any desired direction to give clear visualization of the submucosal layer. Because two scopes were inserted together into the stomach *via* the oral cavity, ESD was undertaken under general anesthesia. Ahn *et al*[24] reported transnasal endoscope-assisted ESD, which is a traction method using two scopes. The nasal scope is used as the traction scope. This method reduces friction between the two scopes in the oral cavity. The disadvan-

tages of the procedure include nasal bleeding due to the transnasal access and the requirement for two endoscopists. Uraoka *et al*[25] reported thin endoscope-assisted ESD. The traction was obtained by using a thin endoscope in the large intestine. This system uses the thin endoscope as lifting forceps to obtain traction in the desired direction. Thin endoscope-assisted ESD has been limited to the rectum and rectosigmoid colon due to difficulty in intubating the second endoscope to the oral side of the distal sigmoid colon. The thin endoscope is not stiff enough for deep intubation. Another limitation is the need for a second endoscopist to operate the traction system.

Countertraction tool attached to the endoscope: An advantage of this method is that it uses a single scope, thus the preparations for the device are comparatively simple. Furthermore, it is not difficult for the operator to achieve countertraction, because the countertraction tool is attached to the endoscope. One disadvantage is that the direction and strength of countertraction is affected by the movement of the scope.

Yamamoto *et al*[26] developed an ST hood which is clear and placed on the tip of the scope. The ST hood prevents tissue from adhering to the scope lens to allow clear observation of the cutting line. At the same time, the ST hood opens the cutting line and exerts countertraction in the local area. However, the field of view is limited to a small area. Endoscopic submucosal dissection with sheath-assisted countertraction was reported by Hijikata *et al*[27]. This method uses 2 channel scopes and a sheath which lifts the lesion and exerts countertraction in the cutting area. The sheath uses one channel and the knife uses the other channel. A TxHood was developed by Kawano *et al*[28]. It can include various therapeutic and treatment tools such as an electric needleknife, a snare wire, an injection needle, and a water jet line, and the lines can be selected freely before insertion of an endoscope covered with the TxHood. Using the grasping forceps from the TxHood, the lesion is lifted to make the cutting line clear.

The therapeutic endoscope we use (the "R-scope") was developed by Yonezawa *et al*[29]. This instrument is equipped with a multibending system and has two movable instrument channels: one moves a grasping forceps vertically for lesion countertraction; the other swings a knife horizontally for dissection. We have also employed the angler fish-type countertraction system[30]. This device has a fine spring grasper which works as the fishing rod to lift up the desired lesion.

Countertraction tool independent of the endoscope: The benefit of this approach is that the direction and strength of countertraction is not affected by the movement of the scope because the countertraction tool is independent of the endoscope. Preparations differ greatly for each method, and are associated with both advantages and disadvantages.

Kondo *et al*[31] reported percutaneous traction-assisted EMR which uses a type of forceps which penetrates the abdominal and gastric walls to provide countertraction. With this method it is easy to coordinate the strength and direction of the countertraction. However, there is a risk of pneumoperitoneum and peritonitis. von Delius *et al*[32] reported percutaneously-assisted endoscopic surgery using a new PEG-minitrocar for advanced endoscopic submucosal dissection. The device is inserted using a PEG technique through the skin and stomach wall, and pulls on the lesion. This system seems similar to the above mentioned percutaneous traction-assisted EMR. The magnetic anchor system was reported by Kobayashi *et al*[33]. It requires the use of a magnetic control system. This uses magnetic force and it is able to change the direction and strength of countertraction. However, this system is large and because it depends on the use of magnetic force, it is not appropriate in patients fitted with a pacemaker. The external grasping-type forceps were reported by Imaeda *et al*[34]. These forceps pull the specimen to obtain countertraction. The direction of countertraction is limited, because the countertraction tool can only be used to pull and push the tissue of interest. This type of forceps is used from the outside so it is unlikely to be affected by the movement of the scope. The medical ring system was reported by Matsumoto *et al*[35]. It uses a ring and makes countertraction. This tool is compact and can pass the forceps channel of the scope, and achieves countertraction during local traction of a tumor. The clip-band technique was reported by Parra-Blanco *et al*[36]. This method uses a rubber band to make countertraction. This rubber band was originally used for orthodontic treatment. The author carefully determined the size of the ring in accordance with ESD. This system is easy to prepare and inexpensive. Chen *et al*[37] reported internal traction using a nylon loop that was attached to the tumor edges with hemoclips. The loop anchored by the 2 hemoclips was tightened by pulling the smaller loop with the hot biopsy forceps, and local countertraction is provided by rolling up the tumor. Li[38] reported the pulley method of ESD which can change the direction of the traction by using a pulley in the stomach. The pulley method with standard clips and dental floss was used to provide traction to improve visualization of the dissection plane during ESD. Jeon[39] reported peroral traction-assisted ESD. A thread is inserted orally to pull a lesion to make countertraction. After circumferential mucosal cutting, one hemostatic clip, tied with a white silk suture, was applied at a site of the lesion suitable for oral traction. During submucosal dissection, the applied suture material was pulled to the oral side.

We have introduced and performed spring-assisted ESD in which countertraction is applied with a spring[40]. A spring is introduced into the stomach through the forceps channel. One end of the spring loop is fixed to the tumor with a clip. The loop at the other end of the spring is fixed with a clip to the intact mucosa on the

opposite side. The submucosal layer is dissected under adequate countertraction force. Our newly introduced countertraction device can be easily handled by one endoscopist, and shows sufficient effective traction distance in any desired direction without interference by the gastroscope movements. The device was helpful for dissection of the submucosal layer without complications and hemostatic treatment.

CONCLUSION

ESD is a very effective treatment for early gastric cancer, but there are many complications. It is thought that we can reduce complications and treatment time through the use of various innovative devices. We think that the countertraction device will become an important device in the future.

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GUIDELINES FOR BASIC SCIENCE

Outcomes research in gastroenterology and endoscopy

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Abstract

Although the field of outcomes research has received increased attention in recent years, there is still considerable uncertainty and confusion about what is "outcomes research". The following editorial is designed to provide an overview on this topic, illustrate specific examples of outcomes research in clinical gastroenterology and endoscopy, and discuss its importance as a whole. In this article, we review the definition and specific goals of outcomes research. We outline the difference between traditional clinical research and outcomes research and discuss the benefits and limitations of outcomes research. We summarize the types of outcomes studies and methods utilized for outcomes assessment, and give specific examples of the impact of outcomes studies in the field of gastroenterology and endoscopy.

Key words: Clinical research; Outcomes; Outcomes research

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INTRODUCTION

The contemporary outcomes research movement in the United States began about three decades ago when an increasing emphasis on cost reduction led to interest in determining and obviating unnecessary procedures. The movement was induced by the discovery of substantial variation in medical practice based on geography and race, with no observable differences in health outcomes[1]. This movement was further propagated by the evidence of inconsistent use of diagnostics, rising healthcare costs and concerns about adverse effects on quality of care from changes in healthcare reimbursement models[2]. These discoveries lead us to realize that there were deficits in our understanding of the safety, indications, and efficacy of medications and diagnostics, as well as therapeutic procedures. It can be assumed that some interventions produce better outcomes than others given these variations in practice and differences in results.

Outcomes research has been defined as "the scientific study of the result of diverse therapies used for particular diseases, conditions, or illnesses". The specific goals of this type of research are to create treatment guidelines, document treatment effectiveness and to study the effect of reimbursement policies on outcomes[3]. In addition to measuring clinical and physiological endpoints, outcomes studies may assess the effects of an intervention on health-related quality of life, functional status, patient satisfaction, and cost[4].

Although overlap clearly exists, outcomes research is different from traditional clinical research in its focus and methods. Outcomes research tends to be observational rather than experimental, and it is patient-centered as compared to clinical research which is more disease-centered. Outcome measures concentrate more on processes

Table 1 Differences in focus between outcomes research and traditional clinical research

	Outcomes research	Traditional clinical research
Focus	Observational	Experimental
Example	Retrospective analysis assessing the factors associated with mortality in patients with severe acute pancreatitis	Randomized placebo-controlled trial of drug X administered to patients presenting with severe acute pancreatitis
Focus	Patient-centered	Disease-centered
Example	Long-term outcomes in patients with dysplastic Barrett's esophagus treated with radiofrequency ablation	Detection of subsquamous intestinal metaplasia ("buried Barretts") on repeat surveillance esophageal biopsies
Focus	Socioeconomic factors	Physiological factors
Example	Survey study assessing the impact on quality of life in teenaged patients diagnosed with ulcerative colitis (UC)	Retrospective analysis on postoperative complications in patients with UC undergoing total proctocolectomy

and delivery of care rather than on drugs and instruments. It aims to study the impact of diseases on patients rather than the mechanisms of disease, and it measures the effects of socioeconomic factors, not the effect of biochemical and physiological factors (Table 1).

Outcomes studies can help physicians in advising patients about what works, what doesn't, when in the course of illness does it begin working, and what it costs to actually work in the real world of clinical practice. These data can help physicians, payers and patients make rational, insightful choices on medical care-related issues[5]. The outcomes research movement is gaining momentum with the recognition of its importance by physicians, specialty medical societies and managed care organizations. This movement towards assessment and accountability has been termed the "third revolution in medical care"[6].

Outcomes research, however, has its own limitations[7]. Applying outcomes research data is difficult when making complex and individualized patient care decisions. In addition, very few of the commonly used and continuously evolving procedures and devices used in medicine are supported by evidence from randomized controlled trials, given that these trials often cost millions of dollars and frequently last years in duration. Finally, compliance with practice guidelines (put forth as a result of outcomes research) is extremely difficult to assess throughout the medical community as a whole.

Outcome measurements in outcomes research may be evaluated based on the categories of clinical measures, economic measures or humanistic indices. Clinical measures include data for clinical events (e.g., need for repeat hospitalization following an upper GI bleed), physiological measures (e.g., assessing acid reflux by esophageal pH measurement studies) or mortality. Economic measures include direct and indirect medical costs (e.g., outpatient visits, work loss, *etc.*), and analyses of resource use. Humanistic indices evaluate symptoms, functional status (e.g., health-related quality of life) and patient satisfaction. Appropriateness of medical interventions, conformance to standards of care or shifts in practice patterns may also be evaluated. In short, outcomes research uses a variety of methods and the following paragraphs provide a general summary of the extent of research embraced by this field of interest.

OUTCOMES ASSESSMENT USING LARGE ADMINISTRATIVE DATABASES

Data collected for billing and coding or management purposes might contain valuable objective data such as cost, length of hospital stay, outpatient visits, resource use or mortality. These data can be analyzed promptly and cheaply without requiring patient consent or interfering with the doctor-patient relationship. Medicare, Medicaid and large private databases have been extensively used to investigate a variety of outcomes such as the risk of re-hospitalization for patients using clopidogrel with a proton pump inhibitor[8], or the disparities in demographics among hospitalized patients with pancreatitis-related mortality[9].

The surveillance, epidemiology, and end results (SEER) program of the National Cancer Institute provides considerable information on cancer statistics not available for other digestive conditions. For example, in 2004 approximately 233 000 people were diagnosed with digestive system cancers, representing 18% of all malignancies[10]. A recent analysis of the SEER database revealed that patients with early esophageal cancer managed with endoscopic therapy have equivalent long-term survival compared to those treated with surgical resection[11]. These types of data are generally limited by quality and completeness of the available information. Detailed clinical information is lacking as it is collected for administrative purposes. Nonetheless, when exercised cautiously by seasoned researchers, analysis of such data can provide important evidence-based information to supplement randomized controlled trials, or provide the framework for other clinical studies.

DECISION ANALYSIS

Decision analysis is the methodology of using mathematical computation for the evaluation of clinical decisions. It is used to ascertain best strategies when there are several different courses of action, and an indefinite or hazardous pattern of outcomes. A decision-tree is created after identifying all accessible choices and likely outcomes. The tree is used to symbolize the available strategies and the likelihood of occurrence of each outcome if a particular strategy is selected. Decision analysis is used to identify the crucial factors in the decision-making exercise and can be used to make healthcare policy recommendations and develop clinical management guidelines. For example, decision analysis played an important role in the development of the current American College of Gastroenterology guidelines[12] for the management of dyspepsia[13].

META-ANALYSIS

A meta-analysis combines the results of several clinical studies which address a set of related research hypotheses that meet pre-determined standards of quality. An expertly conducted meta-analysis can improve statistical power if the sample size of individual studies is small. Meta-analyses are becoming increasingly important in the determination of clinical efficacy and harm, to plan future studies and to make clinical recommendations for therapy. It is an important source of outcomes data for the practice of evidence-based medicine. For example, a meta-analysis of the role of endoscopic variceal ligation in the primary prophylaxis of esophageal variceal bleeding[14] was instrumental in formulating the American Association for Study of Liver Diseases guidelines for the prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis[15].

COST-EFFECTIVENESS ANALYSES

Cost-effectiveness analysis is a form of economic analysis that compares the relative costs and outcomes of two or more courses of action to determine the most productive use of limited resources. The cost-effectiveness ratio evaluates alternative patient management strategies, programs or services. The most commonly used outcome measure is quality-adjusted life years. This type of analysis is a measure to critically evaluate clinical practices and weigh outcomes against their costs. These data can be used for the distribution of limited funds. Such studies have also been used to compare the cost-effectiveness of practices in gastroenterology with the cost-effectiveness of other medical practices. For example, colonoscopy has been compared with computed tomographic colonography in cost-effectiveness studies[16].

HEALTH SERVICES RESEARCH

The measurement of health status, patient preferences, and quality of care are a part of health services research[17]. Health services research examines how people gain access to health care[18], how much care costs, and what happens to patients as a result of this care. The main goals of health services research are to identify the most effective ways to organize, manage, finance, and deliver high quality care, as well as to reduce medical errors and improve patient safety[19].

The measurement of quality of life is also an important topic of research under health services research. General and specific quality of life measures have been developed for research purposes. The Crohn's disease activity index[20], the Harvey-Bradshaw index and the Inflammatory Bowel Disease Questionnaire are examples of such measures. Health services research also encompasses measurement of healthcare use. For example, does early endoscopy alter healthcare use patterns or satisfaction in patients with dyspepsia [21]?

CLINICAL GUIDELINE DEVELOPMENT

Due to wide-spread cost containment measures, clinical guidelines detailing healthcare recommendations have become abundant, however, these guidelines have been based on varying degree of scientific evidence. The Agency for Healthcare Research and Quality (AHRQ) has defined strict criteria for the development of guidelines. Guidelines should be based on robust scientific evidence rather than on expert opinion. It has not been shown conclusively that guidelines change physician behavior. Reasons for this finding may be because some guidelines may not be designed for community physicians, the practicing physicians may disagree with the expert opinion of the guideline author or they may elect not to follow the guidelines because of fear of litigation.

RANDOMIZED CLINICAL TRIALS

Randomized clinical trials (RCTs) are generally considered the gold standard in clinical research. For example, the National Polyp Study was the landmark randomized clinical trial to evaluate effective surveillance of patients discovered to have one or more colorectal adenomas[22]. Traditional RCTs encompass efficacy studies which generally have a strict code of conduct and require predefined hypotheses, randomization of carefully selected subjects to pre-specified intervention arms, largely similar populations, experienced investigators, a specific protocol, a comparable intervention and intense follow-up. Results from these types of studies are robust. However, because of the restrictive design, the results may not be valid in community practice.

On the other hand, outcomes research focuses on effectiveness studies which are designed to evaluate interventions in community settings with unselected patients, typical care providers and usually-performed procedures. Effectiveness studies are often observational and retrospective, without randomized allocation of patient population. Selection bias may be a problem in such studies and adjustment for severity of illness and case mix is an important aspect to retain validity.

CLINICAL EPIDEMIOLOGY

Clinical epidemiology employs rigorous epidemiological methods to study diagnoses, effective management, and natural progression or prognosis of diseases. Clinical epidemiologic studies such as observational studies help in the development of guidelines in the absence of randomized clinical trials[23,24].

IMPORTANCE OF OUTCOMES RESEARCH TO GASTROENTEROLOGY

Digestive diseases have a heavy medical, social, political and economic burden in the United States. In 2004, the

direct health care costs of digestive diseases were more than $97 billion, up from $40 billion in 1985. The total cost of digestive diseases, including direct and indirect, in the United States in 2004 was estimated to be $141.8 billion. More than 72 million ambulatory care visits with patients with a first-listed diagnosis of a digestive disease were reported in 2004. Digestive diseases were also common diagnoses at hospital discharge with approximately 4.6 million discharges of patients with a first-listed diagnosis of a digestive disease and 13.5 million discharges with a digestive disease as a primary or secondary diagnosis. In 2004, there were > 236 000 deaths in the United States with a digestive disease as an underlying cause, which represented 9.8% of all deaths[25].

It is estimated that > 20 million upper and lower endoscopies are performed yearly in the United States[26]. There is no single national database that can provide accurate, population-based information on the absolute number of gastrointestinal (GI) endoscopies and their indications and diagnostic outcomes. To bridge this important gap in knowledge on the burden of GI disease, a National Endoscopic Database (NED) has been started by the Clinical Outcomes Research Initiative (CORI).

CORI was developed to study outcomes of GI endoscopic procedures in "real life" settings with the primary goal to use the NED to acquire information that will improve the quality of clinical practice in gastroenterology. Physicians participating in the CORI consortium produce GI endoscopy reports using a specialty electronic health record. Data from the reports are sent electronically to a central data repository where they are pooled with data from other consortium participants in the NED. The CORI project began in 1995 under the auspices of the American Society for Gastrointestinal Endoscopy. In 2007, the NED received over 250 000 reports from 70 practice sites in 24 states with approximately 400 participating endoscopists. Practice sites include hospitals, ambulatory care centers, private practices, universities, and Veteran's Affairs hospitals. The NED now contains close to 2 million reports[27]. These data have been analyzed to examine endoscopic practice patterns, to develop research hypotheses, to support quality measure reporting, and as a resource for prospective research on topics such as colon polyp surveillance. Although the participating sites are over-represented by veteran and military facilities, the patterns of endoscopy in NED have been shown to be quite similar to that of a national sample of the Medicare population and may well be applicable to the United States as a whole[28].

CONCLUSION

No longer just the domain of a small group of researchers, outcomes research has altered the culture of clinical practice and health care research by changing how we assess the end results of healthcare services. In doing so, it has provided the foundation for measuring the quality of care. The results of AHRQ outcomes research are becoming part of the "report cards" that purchasers and consumers can use to assess the quality of care in health plans[29]. For public programs such as Medicaid and Medicare, outcomes research provides policymakers with the tools to monitor and improve quality both in traditional settings and under managed care. Outcomes research in this regard can be the key to knowing how we better achieve and deliver quality healthcare.

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GUIDELINES FOR CLINICAL PRACTICE

Post-endoscopic retrograde cholangiopancreatography complications: How can they be avoided?

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) has a significant complication rate which can be lowered by adopting technical variations of proven beneficial effect and prophylactic maneuvers such as pancreatic stenting during ERCP or periprocedural non-steroidal anti-inflammatory drug administration. However, adoption of these prophylactic maneuvers by endoscopists is not uniform. In this editorial we discuss the beneficial effects of the aforementioned maneuvers.

Key words: Acute necrotizing; Anti-inflammatory Agents; Catheterization; Cholangiopancreatography; Complications; Endoscopic retrograde; Non-steroidal; Pancreatitis; Stents

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic procedure which has a high complication rate ranging from 5%-40% in different series depending on the difficulty of the examination, previous diagnosis and patient comorbidities. These complications develop mainly as a consequence of papillary maneuvers to achieve deep biliary or pancreatic duct cannulation.

Nowadays, ERCP has entered a new era in which related procedures only fit therapeutic intention. It is not ethically justified to offer such risky exploration to patients intended only as a diagnostic procedure. Thus, patients may be exposed to these risks when the intention of the procedure is to offer a minimally invasive exam with excellent results, thus avoiding surgery or radiologic interventions.

However, in recent years this morbidity has declined due to the benefits of different maneuvers which have allowed this technique to be performed with greater security. This article presents and discusses factors which can help to reduce the morbidity of ERCP, including both non-technical factors, and therefore, endoscopist-independent, and technical factors, and therefore, endoscopist-dependent. In the latter we will include the role of the different cannulation techniques and their influence on post-ERCP morbidity. With regard to non-technical factors, we will review the role of two methods which have accumulated scientific evidence in the prevention of post-ERCP pancreatitis such as pancreatic stent placement and administration of non-steroidal anti-inflammatory drugs (NSAIDs).

REDUCING MORBIDITY BY MEANS OF NON-TECHNICAL FACTORS

We consider endoscopist-independent prophylactic factors as those factors which have proven prophylactic benefit, such as pancreatic stent placement and administration of NSAIDs and antibiotics. The first two factors are used in the prophylaxis of post-ERCP pancreatitis and the latter in the prophylaxis of post-ERCP cholangitis and other infectious complications.

Pancreatic stent placement in various studies was proved to be effective in preventing the development of post-ERCP pancreatitis. Several meta-analyses have also been published, the first in 2004 which included 5 studies and 481 patients[1]. This meta-analysis showed that the incidence of post-ERCP pancreatitis was significantly lower in the stented group (5.8%) versus the control group (15.5%), with an odds ratio (OR) of 3.2 and the number of patients needed to treat (NNT) to prevent pancreatitis was 10. A subsequent meta-analysis included a sixth randomized controlled trial, with similar results[2]. In the stented group the incidence of acute pancreatitis was 12% *vs* 24% in the control group, with a protective OR of 0.44 for the stented group and a NNT of only 8. The final meta-analysis was published recently and included 8 randomized controlled trials which demonstrated a reduction in the OR to 0.22 (95% CI: 0.12-0.38, $P < 0.01$) in the stented group and a NNT of 8 patients[3].

These results have not gone unnoticed in scientific societies, and the European Society of Gastrointestinal Endoscopy includes the recommendation to place prophylactic pancreatic stents in high-risk patients undergoing ERCP[4]. This group of high-risk patients is not well defined, although there is a consensus to consider the following high-risk patients: patients undergoing ERCP for sphincter of Oddi dysfunction, young women, patients with previous history of pancreatitis, patients in whom a high number of pancreatic duct cannulations and injections have been made during cannulation or ampullectomy, and many authors advocate the introduction of a prophylactic pancreatic stent when using the double-wire technique.

The recommended stent is currently a short ($\leqslant$ 5 cm) 5F plastic stent, and preferably with only an external flange, although some authors prefer to introduce double flanged stents[5,6]. Up to 10 d after stenting, observations for spontaneous migration should be made and if present, the stent should be endoscopically extracted.

However, it is not always easy to insert a pancreatic stent and complications related to pancreatic duct cannulation to insert the stent can occur. Therefore, prophylactic pancreatic stenting is recommended when the endoscopist's success rate for this maneuver is higher than 75%[4].

Currently, there are four prospective studies evaluating the utility of prophylactic administration of NSAIDs for post-ERCP pancreatitis, which have been evaluated in three meta-analyses[7-9]. These data have shown that the rectal administration of 100 mg of diclofenac immediately after ERCP, or 100 mg of indomethacin immediately prior to ERCP, significantly decrease the risk of post-ERCP pancreatitis from 12.5% to 4.4%, with a risk reduction of 0.33 and an NNT of 15 patients. Furthermore, in published studies no adverse effects attributable to NSAIDs have been described.

The use of NSAIDs peri-ERCP is indicated in low-risk cases to prevent the development of post-ERCP pancreatitis[4] and probably, although this has not been assessed, in patients at high risk in whom a prophylactic pancreatic stent could not be inserted.

The prophylactic use of antibiotics before or after ERCP to prevent the development of post-ERCP cholangitis or other infectious complications has been extensively evaluated in numerous studies. The British Society of Gastroenterology guide for antibiotic prophylaxis in gastrointestinal endoscopy has recently been published and recommends the prophylactic administration of antibiotics during ERCP in patients who are in the following situations: patients who are not expected to obtain full patency of the bile duct by one ERCP, patients with advanced hematologic cancer, patients with a history of liver transplantation, patients with pancreatic pseudocysts and patients with severe neutropenia[10].

Quinolones are the recommended antibiotics, although the antibiotic and regimen should be tailored to the antimicrobial resistance profile of each hospital.

Confirmation that the best predictor of the development of post-ERCP infectious complications is incomplete resolution of biliary obstruction was subsequently confirmed in a meta-analysis which included nine prospective randomized studies with a total of 1573 patients[11]. According to this meta-analysis, prophylactic antibiotic therapy halved the risk of bacteremia (RR: 050, 95% CI: 0.33-0.78) after ERCP, but did not show any effect on overall mortality (RR: 1.33, 95% CI: 0.32-5.44). In the subgroup of patients in whom ERCP completely resolved the biliary obstruction, the protective effect of antibiotics had no impact. In contrast, the subgroup of patients in whom biliary obstruction could not be resolved completely with ERCP benefitted from antibiotic prophylaxis.

REDUCING MORBIDITY BY MEANS OF TECHNICAL FACTORS

Of the endoscopist-dependent protective factors we can include all the described cannulation variations which have proved beneficial in the incidence of post-ERCP complications. The first factor is undoubtedly the guidewire cannulation technique. This technique was introduced by Siegel and Pullano in 1987[12]. Cannulation with a guide-wire consists of the introduction of a guide-wire into the bile or pancreatic duct instead of contrast injection as the first maneuver. There are several variations of this technique, and the tip of the catheter or sphincterotome is inserted initially with which we will cannulate a

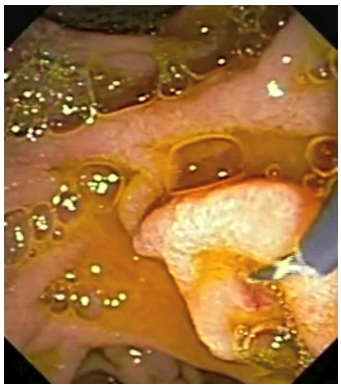

Figure 1 The guide-wire technique has been used in this patient to cannulate the minor papilla. The minor papilla is cannulated with the guide-wire tip protruding a few millimeters over the cannula.

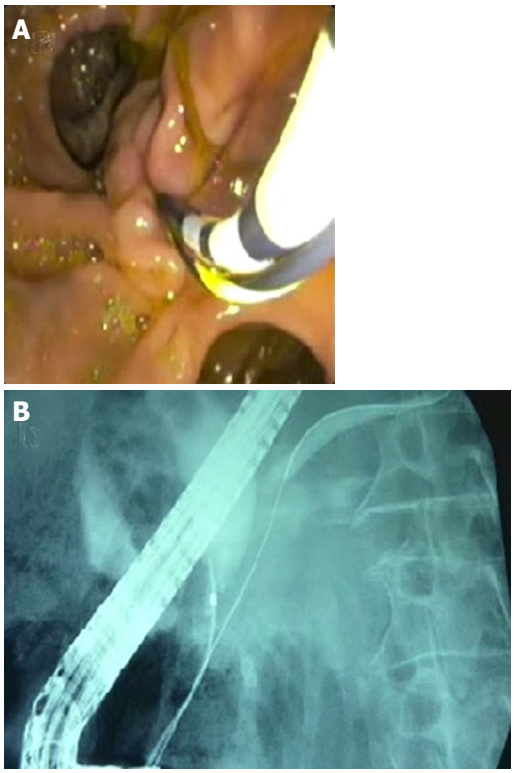

Figure 2 Image of the double guide-wire technique. A guide-wire is inserted in the pancreatic duct and left *in situ*. The cannula is then inserted parallel to the pancreatic guide-wire (A) in order to cannulate the bile duct (B).

few millimeters through the papillary orifice and then introduce the guide-wire to the target. Another variation is direct cannulation with the guide-wire hovering a few millimeters or even one or two inches through the catheter or sphincterotome. This latter option is especially useful in pancreatic cannulation through the minor papilla (Figure 1).

The benefit of this technique compared with classic contrast cannulation has been demonstrated in several studies which show similar results and have been jointly analyzed in a recent meta-analysis[13,14]. This meta-analysis included 5 studies and 1762 patients, and demonstrated that the use of the guide-wire technique significantly improved the primary cannulation rate from 74.9% to 85.3% (OR: 2.05, 95% CI: 1.27-3.31) and more importantly, significantly reduced the incidence of post-ERCP pancreatitis from 8.6% to 1.6% (OR: 0.23, 95% CI: 0.13-0.41). Consequently, the authors concluded that the guide-wire technique should be considered the standard cannulation technique.

The double-wire cannulation technique was first described by Dumonceau *et al*[15] in 1998. It can be used when access to the pancreatic duct can only be achieved during a biliary ERCP. A guide-wire is placed into the pancreatic duct and parallel to this guide-wire a catheter or sphincterotome is inserted to cannulate the bile duct (Figure 2). The functions and benefits attributed to this technique are that the guide-wire in the pancreatic duct could open a stenotic papillary orifice, stabilize the papilla, raise the papilla towards the working channel of the endoscope, rectify the pancreatic and common duct, drain the pancreatic duct and minimize the injections into the pancreatic duct.

One of the first studies evaluating this technique compared a group of 27 patients with difficult cannulation who underwent this technique with another group of 26 patients in whom the endoscopist persisted in trying the classical contrast injection technique. The double-wire technique significantly improved the rate of cannulation to 93% *vs* 58% achieved with the classic technique ($P = 0.0085$), showing no significant differences in the incidence of post-ERCP pancreatitis[16]. However, Ito *et al*[17] did not obtain such good results with this technique and described a cannulation rate of 73% with an incidence of post-ERCP pancreatitis of 12%.

A randomized prospective trial comparing a group of 97 patients with difficult cannulation in whom the double-wire technique was used with another group of 91 patients in whom persistence of classical cannulation was attempted has been published recently[18]. The double-wire technique resulted in a poorer outcome compared with the classical technique regarding the incidence of post-ERCP pancreatitis (17% *vs* 8%, $P > 0.05$), and the cannulation rate was significantly worse with the double-wire technique (OR: 0.66, 95% CI: 0.64-1.12). The authors concluded that the double-wire technique offers no advantage over the classical technique in achieving biliary cannulation, and did not decrease the incidence of post-ERCP pancreatitis.

Therefore, the data available in the literature on this technique are contradictory and at present it is not recommended for achieving cannulation or decreasing post-ERCP pancreatitis. This technique may be useful for achieving biliary cannulation in patients in whom repeated pancreatic duct injections are performed. If this technique is used, a prophylactic pancreatic stent should also be inserted.

A variation of the previous technique is guide-wire cannulation over a pancreatic stent (Figure 3). This technique consists of the introduction of a pancreatic

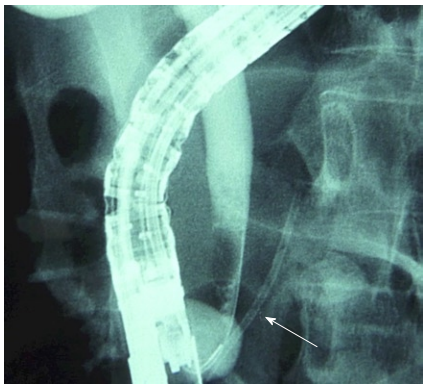

Figure 3 In this fluoroscopic image biliary cannulation over a pancreatic stent technique is shown. The technique resembles the double-wire technique, but a plastic stent (arrow) is inserted in the pancreatic duct instead of the guide-wire, and the bile duct is cannulated in parallel.

stent over the guide-wire initially left in the pancreatic duct, and in parallel with a sphincterotome or catheter to cannulate the bile duct. In a first study, Fogel *et al*[19] reported a significantly lower incidence of post-ERCP pancreatitis in patients with sphincter of Oddi dysfunction in whom a pancreatic stent was placed followed by needle knife sphincterotomy compared with the double-wire technique (10.7% *vs* 28.3%, $P < 0.05$). In a similar group of patients Madacsy *et al*[20] also showed a significant benefit using a pancreatic stent and had no cases of post-ERCP pancreatitis compared with a post-ERCP incidence of 43% in the group of patients in whom the needle knife was performed with a guide-wire into the pancreatic duct ($P < 0.05$).

More recently, Ito *et al*[21] did not find significant differences using the cannulation over a pancreatic stent technique compared with the double-wire cannulation technique regarding primary cannulation (80% *vs* 94%, $P = 0.15$) in a group of patients with difficult cannulation, however, there was a significant benefit in the incidence of post-ERCP pancreatitis (2.9% *vs* 23%, $P < 0.05$).

Therefore, this technique offers a clear protective effect against the development of post-ERCP pancreatitis, and would be recommended when we have access to the pancreatic duct and needle knife sphincterotomy is decided.

Finally, needle knife sphincterotomy (Figure 4) is a well known and validated technique which has different variants: cephalad incision from papillary orifice, pancreatic precut and fistulotomy. Although there are no studies comparing the outcomes of these variants, optimal results with the pancreatic precut technique and fistulotomy technique have been described recently.

The appropriate timing of this technique has been studied. In a recently published meta-analysis including 6 prospective, randomized, controlled trials comparing the rate of cannulation and the incidence of post-ERCP pancreatitis in a group of patients with difficult cannulation in whom early pre-cut was performed (442 patients) with another group in whom persistence in cannulation was performed with late pre-cut if cannulation was unsuccessful (524 patients)[22]. There were no differences in the success rate of cannulation (90.2% *vs* 89.6%, OR: 1.20, 95% CI: 0.54-2.69), however, significant differences were seen in the incidence of post-ERCP pancreatitis (2.48% *vs* 5.34%, OR: 0.47, (95% CI: 0.24-0.91) favoring early pre-cut.

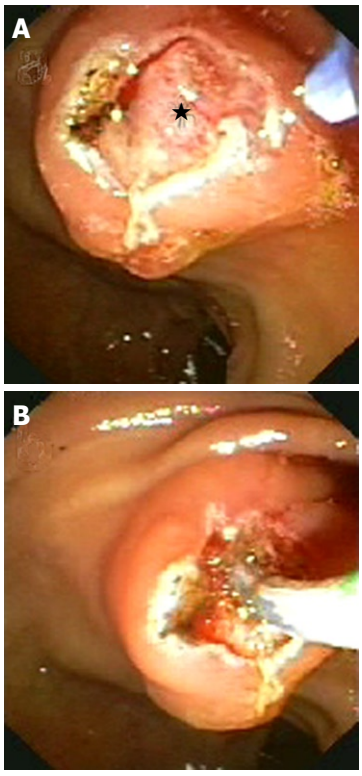

Figure 4 Needle knife sphincterotomy technique. A superficial mucosal cut is performed showing the duodenal portion of the common bile duct as a reddish rounded protrusion (asterisk) (A). A deeper cut is made on this nodule going into the bile duct (B).

Therefore, performing early pre-cut has a similar rate of primary cannulation but is associated with a lower incidence of post-ERCP pancreatitis.

Other endoscopist-dependent factors no less important in our opinion when it comes to reducing the incidence of post-ERCP complications are subjective and difficult to evaluate. These include knowledge update, the progression of more complicated cases and techniques, and cautious attitude of the endoscopist. These factors are extremely important and help to identify not only an appropriate indication for ERCP, but also the different therapeutic techniques performed during this procedure, hopefully contributing to a reduction in the incidence of complications.

CONCLUSION

The acceptance of the aforementioned maneuvers by endoscopists is not uniform. An American survey showed that expert endoscopists are aware of the protective effect of pancreatic stents in patients at high risk, but the indications for stent placement and the type of stent chosen varies widely among endoscopists[23].

A recently published survey showed that up to 21.3% of endoscopists in Europe never perform prophylactic pancreatic stenting despite favorable scientific evidence, mainly because of lack of experience[24]. In this survey it was shown that the vast majority of endoscopists did not regularly attempt prophylactic pancreatic stenting when procedure-related risk factors for post-ERCP pancreatitis were present, and slightly more frequently when patient-related risk factors were present. Moreover, 83.7% of endoscopists do not use NSAIDS for post-ERCP pancreatitis prophylaxis[24].

Expert endoscopists with greater experience in ERCP are more reluctant to adopt changes to their usual technique, probably because they have favorable rates of outcomes and complications, and because they think that introducing an alternative technique into their working methods might lead to a temporary decrease in successful cannulation rates and an increase in complication rates. However, a recent study from Japan has shown that wire-guided cannulation is useful immediately after its introduction in a specialized center with expertise in contrast cannulation, and in this context wire-guided cannulation has a higher rate of primary cannulation, a shorter procedural time and a lower rate of hyperamylasemia[25]. On the other hand, endoscopists with less experience and those in training should know these techniques and adopt them as standard practice given the scientific evidence of benefit.

The question is whether an endoscopist's personal preference is enough reason to maintain a technique? In our opinion it is not, since there is scientific evidence supporting a different policy. Endoscopists in training should adopt the technique proven to be the best. On the other hand, expert endoscopists who reject changes in their technique could argue that they already achieve favorable outcomes. But even good outcomes can be improved and expert ERCPists should be the first to adopt proven variations in technique to obtain clinical improvement.

To conclude, although recommendations in endoscopy should not be rigid and cannot replace clinical judgment[4], it is the duty of both expert and non-expert endoscopists to know their results and complication rates and if these are unfavorable, evaluate which of the previously described variations should be performed to improve their outcomes.

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REVIEW

Pancreatic cystic lesions: How endoscopic ultrasound morphology and endoscopic ultrasound fine needle aspiration help unlock the diagnostic puzzle

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Abstract

Cystic lesions of the pancreas are being diagnosed with increasing frequency, covering a vast spectrum from benign to malignant and invasive lesions. Numerous investigations can be done to discriminate between benign and non-evolutive lesions from those that require surgery. At the moment, there is no single test that will allow a correct diagnosis in all cases. Endoscopic ultrasound (EUS) morphology, cyst fluid analysis and cytohistology with EUS-guided fine needle aspiration can aid in this difficult diagnosis.

Key words: Pancreatic cystic lesions; Endoscopic ultrasound; Endoscopic ultrasound fine needle aspiration

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INTRODUCTION

A search on Medline with the key-words "pancreatic cyst" would find 7074 results, at the time of writing. Why so much interest? There are three answers to this question.

Firstly, there has been an increase in the diagnosis of these lesions, itself a result of improvements in imaging techniques, such as multidetector computerized tomography (MDCT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS). From an autoptic point of view, these lesions are very common. About a quarter of examined pancreases show cystic lesions, 16% of which contain atypical epithelium and 3% high grade dysplasia[1]. Currently, about 1% of patients in hospitals receive, often accidentally, a diagnosis of a pancreatic cystic lesion[2,3]. During imaging tests (MDCT, MRI, EUS) for other reasons, between 13% and 20% of exams will show a pancreatic cystic lesion (PCL)[4] and, more importantly, most of these lesions (90%) are neoplasms with premalignant or malignant features and not pancreatic pseudocysts[5].

Secondly, pancreatic cystic lesions are a large group of varying entities, with a wide variability of biological behavior, from benign to borderline to malignant (Table 1).

Thirdly, and most importantly, until now there has not been a unique test accurate enough to make a differential diagnosis in all of these lesions.

This last point is the focus of this review. We cannot, in fact, make the right decision for our patients if

we are not able to determine exactly what kind of lesion we are studying and so predict the likelihood of developing a malignancy. In the last 10 years we have seen enormous improvements in our diagnostic arsenal. Radiological diagnostic modalities have seen the advent of new CT scans, the emergence of MRI with the help of cholangio-pancreato-RM and, last but not least, the diffusion of EUS, with the possibility of fine needle aspiration (FNA) and analysis of the intracystic fluid. In this review, we will analyze these diagnostic modalities, with particular attention on the EUS aspect of pancreatic cystic lesions, in order to draw some possible and plausible conclusions on the state of the art.

DIAGNOSIS OF PANCREATIC CYSTIC LESIONS

Epidemiological and clinical aspects

Firstly we focus on the prevalence of the different PCLs. Serous cystoadenoma neoplasm (SCN), intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) represent about 90% of all pancreatic cystic neoplasms. These lesions, together with pancreatic pseudocysts (PP), are responsible for 90% of all pancreatic cystic lesions[5-8]. Knowing this, we focus more on these lesions in our diagnostic reasoning.

As in every diagnostic work up in medicine, we start with epidemiological and clinical aspects that in the case of PCLs offer several important indications (Table 2).

SCN represents 32%-39% of all cystic neoplasms[2,9], with a peak of incidence at 62 years of age (although the range is quite wide), a slight prevalence in females (3-4:1)[10] and a slight preference for the pancreatic head (50%)[11]. It is usually asymptomatic unless it is larger than 4 cm, in which case the symptoms are caused by the mass effect. Of the thousands of reported cases in the literature, there are only 26 reported cases of malignancy[12], so it can often be considered a benign lesion.

IPMN represents 21%-33%[2] of all pancreatic cystic neoplasms, although it is likely that its prevalence is greater because of an increase in the diagnosis of small branch duct lesions, particularly in elderly patients. IPMN can involve the main pancreatic duct (MD-IPMN), the branch pancreatic duct (BD-IPMN) or both (MIX-IPMN), although in about 20% of cases such a distinction is not possible[13-15]. In the differential diagnosis of other pancreatic cystic lesions, however, we have to take BD-IPMN into consideration because the classic aspects of MD-IPMN do not require a differential diagnosis with other pancreatic cysts but rather with chronic pancreatitis. There is a slight prevalence in males (60%), with a mean age 65 years, although it can also affect young patients. The most common localizations are the head of pancreas, most often in the uncinate process[15]. Most patients are asymptomatic[16]. When associated with symptoms, IPMN can present with pain similar to chronic pancreatitis, weight loss, jaundice, steatorrhea, diabetes or intermittent acute pancreatitis, which is the sentinel symptom in 15% of cases, both in MD and BD-IPMN[17], due to obstruction of the pancreatic duct with mucin.

Table 1 Cystic lesions of the pancreas[19] (reprinted with permission of Dr. Parra-Herran CE)

Cystic lesions of the pancreas
Non-neoplastic cysts (30%-40%)
No lining
Inflammatory pseudocyst
Paraduodenal wall cyst
Infection-related cyst
True lining
Mucinous non-neoplastic cysts (mucoceles, retention cysts)
Cystic hamartoma
Enterogenous (congenital, duplication) cyst
Endometriotic cyst
Lymphoepithelial cyst
Squamoid cyst of pancreatic ducts
Others (unclassified)
Neoplastic cysts (60%-70%)
True lining
Mucinous lining (30%)
Intraductal papillary mucinous neoplasm (20%)
Mucinous cystic neoplasm (10%)
Serous lining (20%)
Serous cystadenoma (microcystic, oligocystic)
Von Hippel-Lindau-associated pancreatic cyst
Serous cystadenocarcinoma
Squamous lining (< 1%)
Epidermoid cyst within intrapancreatic accessory spleen
Dermoid cyst
Acinar cell lining (< 1%)
Acinar cell cystadenoma
Acinar cell cystadenocarcinoma
Endothelial lining (< 1%)
Lymphangioma
Solid tumors with cystic change (5%)
Solid pseudopapillary tumor
Ductal adenocarcinoma with cystic change
Neuroendocrine tumor with cystic change
Other invasive carcinomas with cystic change
No lining (< 1%)
Mesenchymal neoplasms with cystic change
Others (unclassified)

The risk of malignancy is very high (mean 70%) in MD-IPMN but low in BD-IPMN (mean 25%) and virtually nonexistent in the absence of risk factors, which are clinical symptoms, mural nodes, cyst size > 3 cm, main pancreatic duct dilation over 6 mm and negative cytology[18].

With these first two kinds of pancreatic cystic lesions, there are essentially no clinical and demographic aspects that are of real use for diagnosis.

The frequency of MCNs is reported to range from 10% to 45%[2], although the real incidence is likely less than that of serous cystoadenoma and IPMN[8,19]. MCNs present almost exclusively in females (95%), with a mean age of 53 years (range 19-82 years) and located in 95% of cases in the body-tail of the pancreas[17,18,20,21]. Gender and localization are very important characteristics in the differential diagnosis of pancreatic cystic lesions because they have a high negative predictive value for MCNs.

Regarding potential malignancy, these lesions cer-

Table 2 Major features of four most common cystic lesions

Feature	SCN	MCN	IPMN	Pseudocyst
Prevalent age	Middle aged	Middle aged	Elderly	Variable
Sex	F > M	F[1]	M > F	M > F
Alcohol abuse	No	No	No	Yes
History of pancreatitis	No	No	Frequent	Yes[1]
Location	Evenly	Body-tail[1]	Head	Evenly
Malignant potential	Very rare	Moderate to high	Low to high	None

[1]Mark the most useful epidemiological and clinical information (printed with permission of Dr. M Raimondi). SCN: Serous cystoadenoma neoplasm; MCN: Mucinous cystic neoplasm; IPMN: Intraductal papillary mucinous neoplasm.

tainly have to be considered potentially evolutive. The Sendai International Guidelines[18] recommend resection of all these lesions, although a recent report[21] on 163 resected MCNs showed only 5.5% *in situ* carcinoma and 12% truly invasive carcinoma, less than previously reported, and all malignant lesions were at least 40 mm in size or with nodules.

Pancreatic pseudocysts are quite common, with some reports[22] indicating that they comprise up to 70% of all cystic lesions. However, there are now a number of non-inflammatory small cystic lesions diagnosed with the widespread use of imaging. PPs are slightly more prevalent in males and age is variable. They are evenly distributed in the gland, although the important point is that they are rarely asymptomatic. To formulate a suspicion of pseudocyst, there will almost always be a history of acute or chronic pancreatitis, or at least there will be imaging from CT, MRI or EUS compatible with chronic pancreatitis and a history of alcohol abuse, trauma, recent surgery or family history of pancreatitis. It is now accepted that in patients with no history of acute or chronic pancreatitis, a strong work-up should be done to exclude possible neoplastic cystic lesions before suspecting PPs[22,23].

Finally, although some demographic and clinical characteristics are suggestive of specific lesions and have to be taken into account in the diagnostic evaluation, these characteristics are not sufficient by themselves for a definitive diagnosis in all such lesions.

Imaging characteristics

CT and MRI are the two radiological techniques used for the diagnosis of pancreatic cystic lesions. CT is often the first modality in the diagnosis of these lesions, which are usually detected during exams done for other reasons. The multidetector row CT gives a very good image of the lesions, clearly showing the lesions and the rest of pancreatic parenchyma[24-26]. Some characteristics, such as calcification, can be seen only with this modality. However, a recent review of diagnostic accuracy of CT showed a range of between 20% and 90%[27].

MRI with cholangiopancreatography (MRCP) allows optimal depiction of the internal features of pancreatic cysts, such as septa, cyst contents such as debris, as well as the pancreatic ductal system and its connection to the cyst[26,28-31].

A classification system of cyst morphology[32] has been proposed for narrowing the differential diagnosis and improving the diagnostic yield. Pancreatic cysts can be classified into four subtypes: (1) unilocular cysts; (2) microcystic lesions; (3) macrocystic lesions; and (4) cysts with a solid component. Although this classification is useful, it cannot by itself be used as a final solution for differential diagnoses because of the overlap of morphological aspects of different lesions, especially in small cysts (< 3 cm).

Accuracy of CT and MRI in characterizing cystic pancreatic masses for malignancy has been proven but they have only limited accuracy for the diagnosis of specific lesions (less than 50%)[33,34].

A study of 136 resected patients with incidental pancreatic cysts showed that, on cross sectional imaging (CT, MRI or both), diagnosis was correct in only 63% of cases[14].

Regarding the indications of 18-fluorodeoxyglucose positron emission tomography (PET) in PCLs, a study showed that it is more accurate than the International Consensus Guidelines in distinguishing benign from malignant (invasive and non-invasive) IPMNs[35] but it has no role in determining specific diagnosis of PCLs and there are no studies comparing PET with other diagnostic tools (such as EUS-FNA).

In conclusion, both CT and MRCP are helpful in characterizing cystic pancreatic lesions, with an acceptable accuracy in determining malignancy but low accuracy in determining a specific diagnosis.

More studies are needed in order to determine the role of PET in the management of PCLs.

EUS in cystic lesions

EUS has many features that make it, hypothetically, the ideal tool for evaluating pancreatic cystic lesions. The strict proximity between the transducer and the lesions allows for a very precise definition of the structural component of the cysts and some components of pancreatic cysts, such as the honeycomb pattern or small mural nodules, are better visualized with EUS than with other modalities.

With EUS, it is possible to define cystic localization, size, locularity, internal structural features, mural nodules, contours, cystic wall, pancreatic duct and calcification. One of the problems with this technique related to the morphological aspects of pancreatic cystic lesions is the plurality of terms used by different authors to define them.

Locularity is determined by the presence of septa and can be classified as unilocular (or monolocular) or multilocular (or multicystic). The cystic component can be classified "with microcystic area" or "without microcystic area". The microcystic area is defined as an area where small (less than 2-3 mm each) cysts aggregate (usually more than 6 cysts) separated by thin-walled

Table 3 Endoscopic ultrasound morphology and cystic fluid analysis in pancreatic cystic lesions

	Serous cystoadenoma	Mucinous cystic neoplasm	BD-IPMN	Pseudocyst
Localization				
Head	+++	+/-	+++	++
Body-tail	++	+++	++	++
Locularity				
Unilocular	+	+	+	+++
Multilocular	+++	+++	+++	+
Internal structural features				
Microcystic aspect	+++	-	+	-
Bunch of grape aspect	+	-	+++	-
Countors				
Round	+	+++	+	+++
Lobulated	+++	+/-	+	+/-
Irregular	+/-	-	+++	-
Central scar	+	-	-	-
Visible cystic wall	-	++	+	+/++
Multifocality	-	-	++	+/-
Debris	-	-	-	++
Visible comunication with pancreatic duct	-	-	++	+
Calcification				
Central	+	-	-	-
Periphery	-	+	-	+/-
Solid lesion	-	+	+	-
CEA				
⩾ 192 mg/mL	+/-	++	++	+/-
⩾ 5 mg/mL	+	+++	+++	++
⩽ 5 mg/mL	+++	+/-	+/-	+
Amylase				
> 250 U/L	+	+/++	++/+++	+++
K-RAS mutation	-	++	++	-
Mucin	-	+	+	-
Cytology	Glycogen	Mucinous	Mucinous	Inflammatory

+++: Very frequent; ++: Moderately frequent; +: Infrequent; +/-: Possible but very infequent. BD-IPMN: Branch duct intraductal papillary mucinous neoplasm; CEA: Carcinoembryonic antigen.

septa, producing a honeycomb-like appearance[36].

The contour can be round (or ovoid), lobulated or irregular. Lobulated is defined as the presence of rounded contours that cannot be described as the borders of the same circle[37]. Irregular is defined as the presence of high irregularity in the contours.

The wall cyst is considered thin if it is 2 mm or less and thick if more than 2 mm for at least 25% of the lesion circumference[37].

Specific EUS aspects of a single cystic lesion can be observed (Table 3).

In SCNs, there is controversy over the site of the pancreas most frequently affected[38] but probably these cysts are evenly distributed.

Visualization of the microcystic area within the cyst, located either at the centre of the cyst (Figure 1A) or next to a macrocystic area[36] (Figure 1B) or in the internal septa of the lesions[39] (Figure 1C), is very typical of these lesions. The thin internal septa are hypervascular on Doppler[40]. The best modality for depicting this aspect is EUS. The microcystic area is present in about 85% of SCNs and is highly accurate in the specific diagnosis of these lesions[36]. A central stellate scar (sunburst)[38], sometimes calcified, is pathognomonic but is seen in 20%-30% of cases on MDCT but only in 11% of cases with EUS[39].

The capsule is usually poor developed and there is often a poor distinction between the tumor and the surrounding pancreatic parenchyma[37,39,41].

These lesions usually have lobulated contours[36] (Figure 1C).

In lesions in which the cysts are a few millimeters in size, the tumor can have a solid appearance due to innumerable interfaces[40], the so called "pseudosolid form" (Figure 1D). A third morphological pattern is also known as the "oligocystic variant" with few cystic spaces[40].

Unilocular SCNs with no microcystic component account for about 10% of all these lesions. The only characteristics that can help in identifying these is the absence of a discernible cystic wall[39] and lobulated contour[36,37], although in this case a more reliable diagnostic tool is analysis of cystic fluid.

In SCN, communication with the pancreatic duct is never seen[41].

EUS aspects of MCNs are variable[38]. They are a well defined, single, round[36] (orange like)[18] cyst that can be unilocular[36,37] but more typically present with multiple macrocystic locules (usually less than 6[36], which are usually > 1-2 cm in diameter[39,42,43]) divided by septa[20,36,40,44] (Figure 2A and B) and with no macroscopic communication with the pancreatic duct[18,44]. The aspect is of a "cysts in cyst"[18]. MCNs commonly have a visible cystic wall (< 2 mm)[7,37-39]. Thick mucoid cyst content can appear granulated on EUS[38].

Focally thickened cystic wall or internal septa, clear intramural nodules or solid component, and dilation of the pancreatic duct are associated with invasive malignancy[20,21,45-48]. Goh *et al*[45] reported that none of the 40 malignant (carcinoma *in situ* or invasive) MCNs in his study were < 3 cm; only one was < 4.5 cm (3 cm). In a study by Crippa *et al*[21], all MCNs with cancer were either 40 mm in size or had nodules.

Peripheral wall curvilinear calcifications (egg shell calcification) are characteristic of these lesions, although present in less than 10%-25% of cases[49], and are considered predictive of malignancy[47].

BD-IPMNs (and sometimes MIX-IPMNs) need a differential diagnosis with the other pancreatic cystic lesions. MD-IPMNs most need a differential diagnosis with chronic pancreatitis. The typical aspect of BD-IPMNs is mutiloculated lesion[28,50], with a "bunch of grapes"[18,50] aspect (Figure 3A), produced by multiple secondary pancreatic ducts dilated by mucin. So these aspects produce two important image characteristics of these lesions: firstly, the lesions have "cysts in cyst" aspect[18] different from MCNs, which have a "cyst in cyst" aspect[18]. In addition, these lesions do not have a round shape but do have an irregular contour. A study by Kubo *et al*[36] showed that all MCNs had a round appearance and only 7% of BD-IPMNs appeared round.

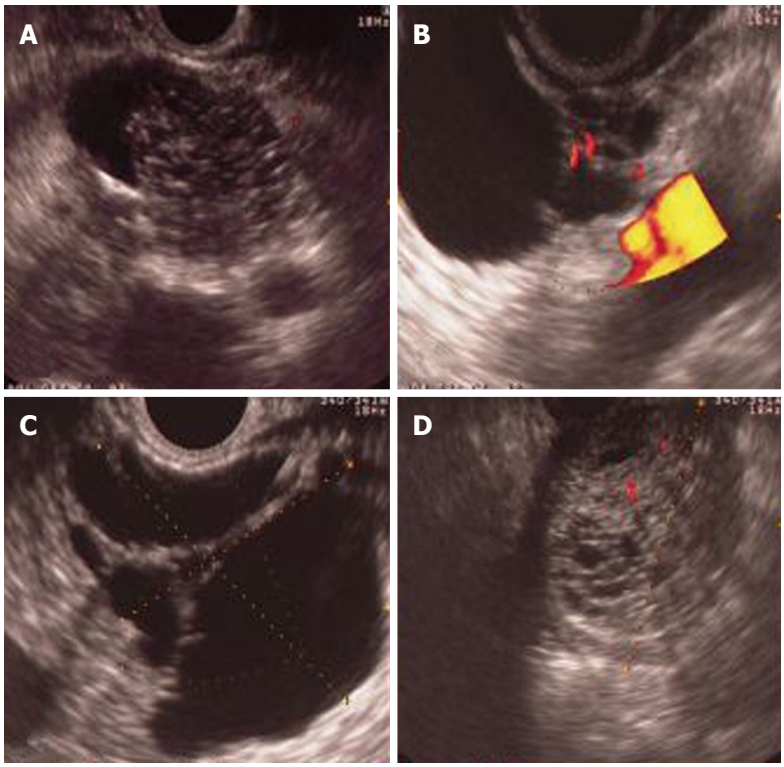

Figure 1 Serous cystoadenoma. A: Microcystic area, centrally located; B: Beside microcystic area; C: Peripheral and internal septa microcystic area, lobulate contour; D: Pseudo-solid form.

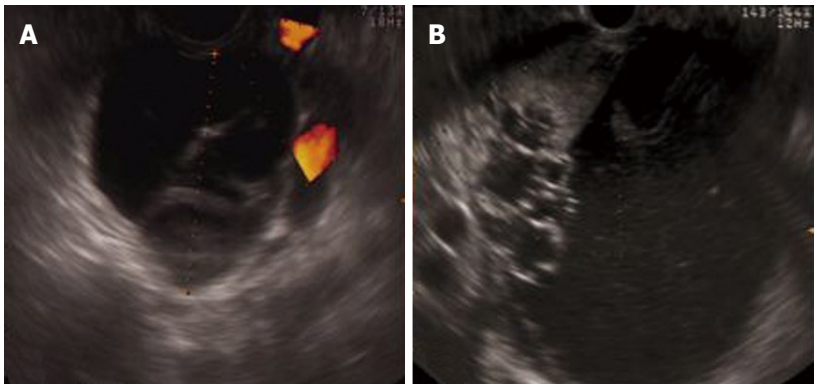

Figure 2 Mucinous cystic neoplasm. A-B: Round lesions with septa (aspects of cysts in cyst with round contour).

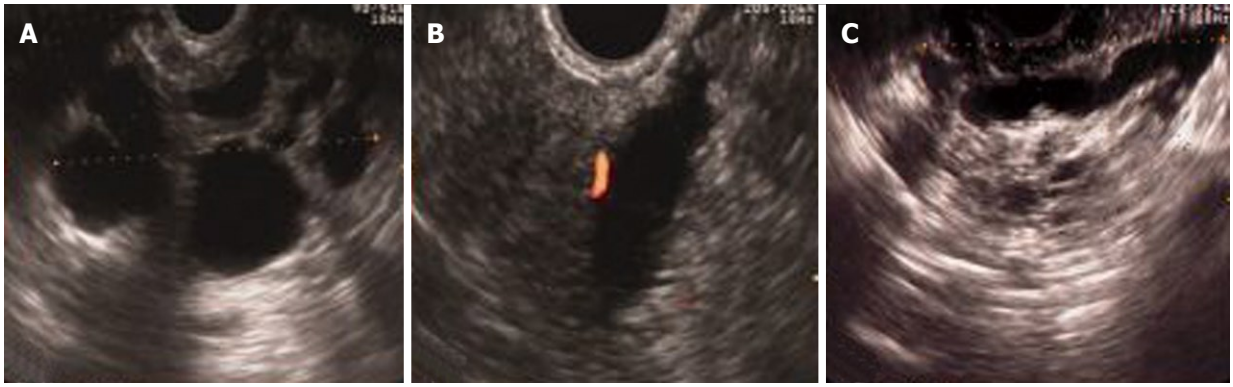

Figure 3 Branch duct intraductal papillary mucinous neoplasm. A: "Bunch of grapes" lesion (cysts by cyst aspects with irregular contour); B: Finger-like aspect; C: Clubbed-like aspect.

Another typical aspect of a BD-IPMN is a cystic lesion composed of finger (Figure 3B), tubular or clubbed-like dilation (Figure 3C) of secondary pancreatic ducts.

All the aspects of BD-IPMNs described above can be seen in the same lesions, so radiologists have called the aspect of BD-IPMNs a "pleomorphic cystic shape",

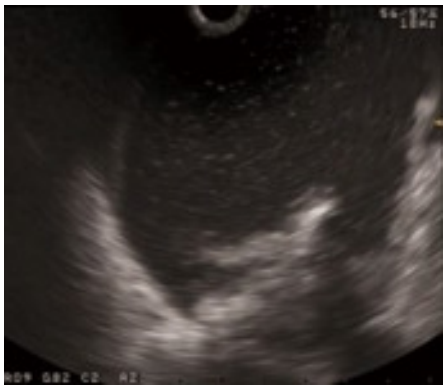

Figure 4 Pancreatic pseudocyst. Round lesion without septa and with visible hyperechoic debris inside.

which is defined as one containing three or more cysts, including oval, tubular or clubbed-finger-like cysts[28,51].

However, these lesions are sometimes formed by only one large ectatic pancreatic secondary duct and in this case the lesions will be unilocular[50,52], round and impossible to distinguish from other unilocular pancreatic cystic lesions by EUS aspect only. One of the most important diagnostic tools for BD-IPMNs is identifying whether there is communication between the lesion and the pancreatic duct. MRI was significantly more accurate than MDCT in identifying this characteristic in one study[13]. However, EUS, although operator dependent, can be very useful, particularly when CT or RMN are equivocal. Kim *et al*[53] demonstrated that there is no difference between MRI and EUS in showing communication between pancreatic cystic lesions and the pancreatic duct.

Another specific sign for diagnosis of IPMNs is the presence of cystic dilation of the small branches of the pancreatic ductal system in two or more areas within the pancreatic parenchyma. Multifocality has been reported in about 30% of IPMN[18] and is quite specific to these lesions because only rarely do other lesions have this characteristic (simple cyst or serous cystoadenoma in Von Hippel-Lindau syndrome, multiple neuroendocrine tumor with cystic aspects, metastasis with cystic pattern). During EUS exams, an endoscopic view of the papilla should be always done to exclude mucin extruding from the patulous papilla (fish mouth papilla), which is diagnostic of IPMN[38], although this phenomenon is present in only 30% of cases, almost all of which with MD or MIX IPMN[15].

Pais *et al*[54] showed that in 74 operated patients, EUS features of a solid lesion, a dilated main pancreatic duct, ductal filling defects and thickened septa were predictive of malignancy in IPMNs.

The most frequent aspect of PPs is a round, unilocular cyst without internal septation or mural nodules, with less than 10%-20% appearing multilocular[23,36]. The appearance of the cystic wall can vary, from imperceptible or minimally visible to that of a uniform thickness[37,47]. Internal debris visible at EUS as hyperechoic material inside the cyst (Figure 4) can be seen floating with change of the decubitus of the patient or during aspiration of intracystic fluid. It is important to look for this characteristic because it is highly specific to pseudocysts. Macari *et al*[55] reported that on MRI, 13 of 14 (93%) pseudocysts had debris but only 1 (4%) of 22 cystic neoplasms had debris. Debris is very easily seen with EUS. Sometimes, MCNs with very viscous mucin can have an intracystic fluid with a granular aspect that looks like debris[38]. Gonzalez Obeso *et al*[23] reported a 22% rate of pseudocysts with internal debris seen on EUS and in this study, a diagnosis of pseudocyst either was suggested or made definitively by the endosonographer for the majority of patients (69%).

Despite the fact that pseudocysts typically communicate with the pancreatic duct, this is often not identifiable on cross-sectional or EUS imaging[52].

A characteristic to be taken into account is that pseudocysts, different from cystic neoplasms, can show rapid changes in the arc in just a few weeks, either rapidly increasing or decreasing, until spontaneous resolution[47,52].

The EUS aspect of chronic pancreatitis (CP) should always be taken in to serious account and, despite some limits, EUS is the most useful single test for evaluating CP[56]. A pancreatic cystic lesion without a history of acute or chronic pancreatitis, or without the presence of a risk factor and imaging clearly diagnostic of chronic pancreatitis, regardless of the EUS aspects, should be considered a pancreatic cystic neoplasm until other tests can definitively exclude it.

A review by Oh *et al*[27] of seven studies[42,57-62] of the diagnostic accuracy of EUS morphology in differentiating cystic lesions of the pancreas, reported results of between 51% and 90%. Furthermore, in one study of videotapes of EUS procedures from 31 consecutive cases[63], there was little more than chance inter-observer agreement among experienced endosonographers on a diagnosis of neoplastic *vs* non-neoplastic lesions, specific type and the EUS features of pancreatic cystic lesions.

The differences result from the intrinsic differences among these studies. Some studies were done to identify whether EUS was able to detect the occurrence of overtly malignant change[42,58], others to differentiate benign from premalignant lesions[60-62], and another to differentiate all subtypes of lesions[59]. All but one[61] were retrospective. Some studies were done of EUS imaging[60] or videotape[63] that may not have completely reproduced the findings as compared with an actual real-time examination and endosonographers were not aware of the history or prior imaging studies. The combination of clinical history and cross-sectional imaging, along with real-time EUS, may increase the contribution of EUS to the characterization of cystic lesions of the pancreas. Definitions of EUS criteria for specific lesions and malignancy were sometimes different among these studies and reflect the lack of a uniform nomenclature for describing the EUS features of cystic lesions.

On the other hand, O'Tool *et al*[39] found EUS to be better in delineating the internal structures of cysts, such

as septa, thick content and mural nodule. The combination of a cystic wall that is thickened and the absence of microcysts had a sensitivity of 100% and specificity of 78% for a diagnosis of MCN compared with macrocystic SCN. Song *et al*[44] showed that absence of septa and mural nodules and the presence of parenchymal change are indicators of a pseudocyst rather than a cystic neoplasm, with 88% accuracy.

More recently, Kubo *et al*[36] observed that 8 of 11 monolocular cystic lesions in his study were non-neoplastic and that 11 of 12 SCNs included microcystic areas. All MCNs were round, while 93% of IPMNs were not. In a multivariate analysis, he concluded that locularity (presence of septa) and a cystic component (presence of microcystic area) were important for a differential diagnosis of potentially malignant cystic pancreatic tumors and that the characteristics of cystic tumors revealed by EUS are useful for differential diagnoses.

There are few studies comparing radiological and EUS accuracy in pancreatic cystic lesions[53,62,64]. Gerke *et al*[62] found an accuracy in classification into benign and malignant or potentially malignant cystic lesions of 66% for EUS and 71% for CT scan, with very poor agreement between them. More recently, Kim *et al*[53] found that there was no difference between the ability of MRI and EUS to correctly classify lesions as cystic or solid (accuracy, 90%-98% *vs* 88%; $P > 0.05$) for the characterization of septa, mural nodule, main pancreatic duct dilatation, communication with the main pancreatic duct and a prediction of malignancy.

EUS-FNA

Linear array echoendoscopy allows for EUS-FNA of solid and cystic lesions. In PCLs, EUS-FNA allows evaluation of extracellular mucin, cytological and sometimes histological analysis, biochemical, tumor markers and molecular analysis[65] and the complication rate for EUS-FNA of cystic pancreatic lesions from a systematic review[66] was slightly more than that for solid ones (2.75% *vs* 0.82%), with pancreatitis being the most frequent. The others were pain and bleeding that were self-limiting, and infection, which has become very rare since the introduction of antibiotic prophylaxis.

The risk of seeding is very low, with only one published case of peritoneal seeding after EUS-FNA of a PCLs[67]. The EUS-FNA techniques for pancreatic cystic lesions are quite simple. The needles normally used are the same as those for solid lesions, 19, 22 and 25 G. Doppler is recommended to avoid puncture of intervening vessels, as is crossing the normal pancreatic parenchyma as little as possible to help avoid pancreatitis. Other recommendations include complete drainage of the cyst in a single needle passage, antibiotic prophylaxis with intravenous antibiotics just before the procedure, followed by the oral route for 3-5 d to reduce the risk of infection.

Only one study with ten patients was done on the use of Trucut biopsy in pancreatic cystic lesions[68], so there is little data on this technique. A recently published prospective study by Hong *et al*[69] described techniques for obtaining more cellularity for cytological diagnosis. This technique consists of attempting to obtain a cystic wall biopsy (CWB) by puncturing the far wall of the cyst and moving the needle back and forth through the wall, after aspiration of fluid from the cyst. The author reports that 81% of the specimens had cellular material adequate for cytological assessment, which was higher than has previously been reported for standard FNA.

A new device, the Echobrush (Cook Medical), was tested in several studies[70-72]. Although better results than those for standard needles have been[70] reported, some limitations have to be considered. The brush takes only a 19 G needle, so stiffness limits its use, especially for lesions in the pancreatic head and uncinate process. In addition, it can only be used for lesions that are at least 2 cm in diameter and a high rate of complications (8%-10%) and one death have been reported[71]. More studies are needed.

A meta-analysis[73] comparing EUS-FNA-based cytology with surgical biopsy or histology and including 376 patients from eleven[42,58,59,61,74-80] studies showed a low sensitivity (63%), but good specificity (88%) in differentiating mucinous cystic lesions from non-mucinous lesions, with a diagnostic accuracy of 89%. However, the authors concluded that review literature on diagnostic accuracy of EUS-FNA-based cytology for pancreatic cystic lesions is limited and heterogeneous, and that well-designed randomized trials are needed in this field.

The largest study of FNA cytology is a prospective cooperative pancreatic cyst study[61] of 112 surgically proven lesions that showed a sensitivity, specificity and accuracy of 34.5%, 83% and 51%, respectively. A prospective two center study to investigate the technical success of EUS-FNA in pancreatic cysts in 143 patients was recently published[81]. de Jong *et al*[81] reported that EUS-FNA was possible in 90% of patients but that cytological diagnosis was obtained in only 31%, due to insufficient cellularity of aspirate liquid, and that biochemical analysis was possible in only 49%, due to insufficient amount of fluid or high viscosity. These numbers are much lower than those reported in another prospective study by Frossard *et al*[59]. In that study, cytological analysis was done in 127 patients with pancreatic cysts and a classifying diagnosis was provided in 98 cases (77%). The authors used the FNA needle to obtain fluid and a mini biopsy, while the cytologist used a liquid-based cytology, the ThinPrep 2000 (Cytyc Corp., Marlborough, MA), a cell preparation processor that provided a monolayered cell population. Both mini biopsy and cyst fluid process may have made the difference in this study, although not all authors agree with the use of liquid-based cytology to process cyst fluid[48].

Greater agreement among cytopathologists and in general among physicians involved in PCL treatment is needed on processing of cyst fluid for cytology.

Looking for the presence of extracellular mucin in

aspirate from PCLs may aid in making a diagnosis, at least in distinguishing mucinous from non mucinous lesions, although it is not present in approximately 50% of mucinous cysts. Although mucin may be visible at aspiration, thick sheets of colloidal-like mucin that cover much of the slides need to be watched for. This type of mucin is sufficient for a diagnosis of mucinous cyst, even if acellular[48]. Mucin stain (alcian blue, mucicarmine) may lead to an erroneous interpretation of wisp mucin from gastrointestinal contaminants as indicative of mucinous cyst. Liquid-based cytology attenuates the appearance of mucin and Pitman *et al*[48] do not recommended it for processing cyst fluid.

Correct execution of sampling[69], an experienced cytopathologist and correct treatment of smears and aspirated fluid[59,73,81] can improve the sensitivity of these tests, although new methods for improving the yield of FNA are needed. The Echobrush or CWB could conceivably improve results, although larger randomized trials are needed to confirm results and safety.

To enhance the diagnostic capability of cytology, cyst fluid can be analyzed for tumor markers and amylase. The overall cystic fluid amount for dosage of tumor markers and amylase is about 0.5 mL for each, so with just 1 mL it is possible to do both tests. Several tumor markers in aspirate from PCLs have been considered: Carcinoembryonic antigen (CEA), CA 19-9, CA 72-4 and CA-125. CEA is considered the most accurate marker in differentiating mucinous from non-mucinous cysts. There is continual debate in the literature over the best cut-off of CEA levels for discriminating mucinous from non-mucinous cysts The value of cut-off ranges from 20 ng/mL to 800 ng/mL in different studies, obviously with greater sensitivity for a low cut-off value and greater specificity for higher ones[27,49]. However, the most frequently utilized cut-off derives from a large prospective study by Brugge *et al*[61] on 112 patients who underwent surgery. It established that a level of 192 ng/mL has a diagnostic sensitivity of 75%, a specificity of 84% and an accuracy of 79% in differential diagnosis of mucinous and non-mucinous cysts. In another pooled analysis from 12 studies, a value of > 800 ng/mL arrived at a specificity of 98%, but a sensitivity of only 48%[82].

Very low values of CEA are extremely useful. CEA levels of less than 5 ng/mL have been found in the pooled analysis of published studies[82] to be highly diagnostic for serous cystoadenomas or pseudocysts (sensitivity 50%, specificity 95%). A retrospective analysis[83] of patients with histologically confirmed cysts showed that cyst fluid CEA of less than 5 ng/mL for a diagnosis of non-mucinous lesions had a sensitivity of 44%, specificity of 96% and diagnostic accuracy of 78%. Very few mucinous cysts have values below 5 ng/mL[83,84].

For pseudocysts there are more widespread values. Rarely do they have a value above 192 ng/mL (5%-14%)[23,83] and only 25% have a value of less than 5 ng/mL[23,83]. In a paper on 21 pseudocysts, the median of intracystic fluid CEA was 41 ng/mL (mean 129 ng/mL) so, compared with serous cystoadenomas, they do have significantly higher levels of cyst fluid CEA[23].

For practical purposes, we can summarize the information on CEA dosage in cystic fluid from different studies: values above 192 ng/mL support the interpretation of mucinous cyst, with increasing specificity mirroring an increase in CEA concentrations. Values lower than 5 ng/mL strongly support a diagnosis of non-mucinous cyst, particularly of serous cystoadenoma. Pseudocysts rarely have values above 197 ng/mL and the median value to be expected is about 40 ng/mL (Table 3). A few reports have suggested that CEA can predict malignancy if it is found to exceed some value (ranging between 200 ng/mL and 5000 ng/mL), with varied specificity and sensitivity, although many large studies[61,82,83,85] have shown that CEA is not useful in differentiating benign from malignant cyst.

Although CEA is not the solution to all diagnostic problems in pancreatic cystic lesions, the 2007 American College of Gastroenterologists Guidelines recommend it as the first test to do if minimal fluid is acquired during aspiration[86].

Amylase levels in pancreatic cystic fluid are used to investigate the possibility that the cyst is communicating with the pancreatic duct. There is no definitive value to demonstrate communication with the pancreatic duct. Values between 250 U/L and 5000 U/L can be found in different studies[82,84].

Amylase values in pseudocysts are usually in the thousands and almost never under 250 U/L[82,83,87]. Amylase values are over 5000 U/L in 3/4 of IPMN[83,84]. In serous cystoadenoma, the amylase value is usually less than 250 U/L[16,82,83], although there are a number of exceptions. MCN very rarely have macroscopic communication with the pancreatic duct, so the expected level of amylase is low in pancreatic cystic fluid[20]. There are several studies[16,83,87] that have shown that amylase intracystic fluid levels in MCN can be elevated, with no differences between IPMN and pseudocysts, perhaps because of diminutive connections between the cyst and the ductal system.

There are some reports that speculate on the presence of malignancy in IPMN and MCN with low levels of amylase in intracystic fluid, assuming that rapid uncontrolled cellular growth could occlude any macroscopic or microscopic ductal connections[83-87]. At present, there are insufficient data for investigating this suspicion.

In summary, we can say that pseudocysts rarely have intracystic fluid values of less than 250 U/L, IPMN have elevated values in 75% of cases, and serous cystoadenomas usually, but not always, have values below 250 U/L. MCN can have widely variable values (Table 3).

Molecular analyses have been done on intracystic fluid. The largest study in this field is the PANDA study[88], which was a prospective, multicenter study to evaluate the role of cystic fluid DNA analysis in differentiating mucinous from nonmucinous cysts. It showed that, in 113 patients with pancreatic cysts, elevated amounts of

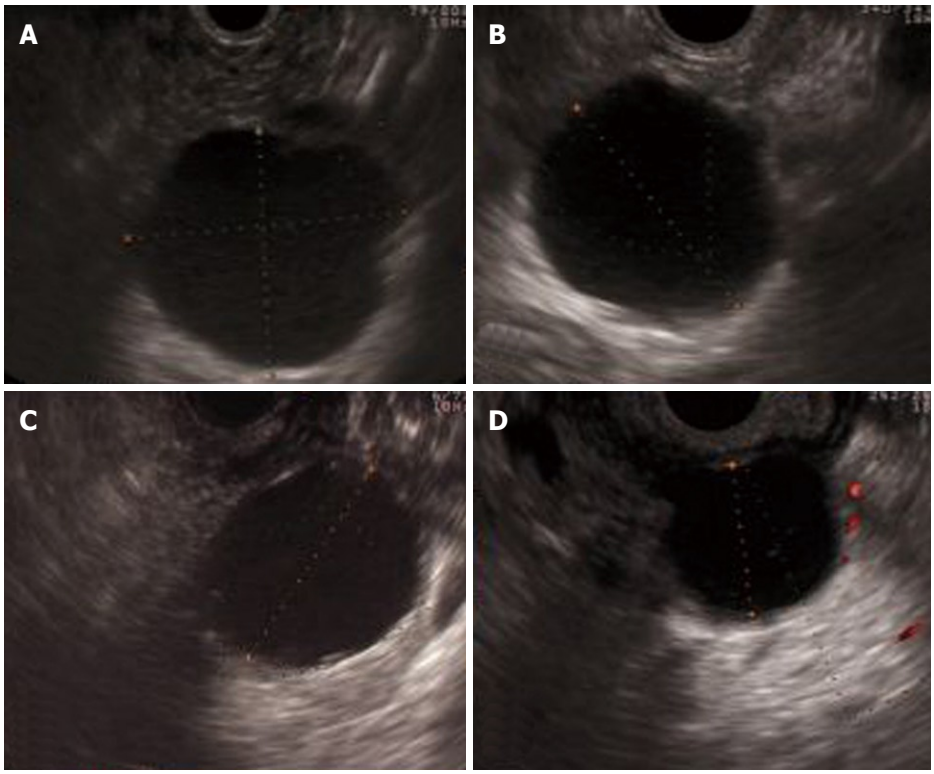

Figure 5 Unilocular aspects in cystic pancreatic lesions. A: Sixty year old female, no symptoms. Lesion in pancreatic head, no visible communication with pancreatic duct. Carcinoembryonic antigen (CEA) 1.5 ng/mL, Amylase 125 U/L, K-RAS mutations negative. Cytology: Cuboidal cell periodic acid-Schiff positive, no mucus. Diagnosis: Unilocular serous cystoadenoma; B: Seventy-nine year old female, no symptoms. Multiple cystic lesion in pancreatic head and tail. Lesion in pancreatic tail with visible communication with pancreatic duct. CEA 12 000 ng/mL, amylase 12 870 U/L, K-RAS mutation positive. Cytology: Mucin and cuboidal cell with mild atypia and papillary arrangement. Diagnosis: Multifocal branch ducts-intraductal papillary mucinous neoplasm; C: Fifty year old female. Lesion in pancreatic body, no visible communication with pancreatic duct. CEA 280 ng/mL, amylase > 15 000 U/L, K-RAS mutation positive. Cytology: Acellular without mucin. Surgical histology: Mucinous cystoadenoma; D: Forty-five year old male, history of alcoholism and recurrent acute pancreatitis. Lesion in pancreatic body. CEA 61 ng/mL, amylase > 15 000 U/L, K-RAS mutations negative. Cytology: Inflammatory cells and pigmented histocytes. Diagnosis: Pancreatic pseudocyst.

pancreatic cyst fluid DNA, high-amplitude mutations and specific mutation acquisition sequences were indicators of malignancy and the presence of a k-ras mutation was indicative of a mucinous cyst.

Another study[89], however, showed a poor correlation between CEA levels and molecular analysis, although the combination of CEA and molecular analysis achieved 100% sensitivity for the diagnosis of mucinous cyst. Molecular analysis needs very small quantities of intracystic fluid (0.4 mL) and is surely a promising test. However, high cost and availability pose some limits. Accuracy of molecular analysis needs to be tested before drawing any definitive conclusions. In addition, reproducibility has to be tested in other laboratories and a cost-benefit analysis for comparison with current tests has to be done.

Glycosylation variants of mucins[90], proteomic analysis[91] and microRNA expression profile[92,93] are among the emerging tests under investigation that could potentially become biomarkers in cyst fluid samples.

CONCLUSION

There is no single test accurate enough to make a sure diagnosis in every pancreatic cystic lesion and so the diagnosis of such lesions is a puzzle, with bits of information deriving from demographic, clinical, radiological, EUS morphological and intracystic fluid analyses.

EUS morphology alone cannot provide for a sure diagnosis in all cases and a recently published paper on inter observer agreement confirms that such agreement is generally low[94]. This same paper also showed that the more expert the endosonographers, the higher the rate of agreement, probably because they "speak the same language". So it is likely that having greater agreement on what to look for and the meaning assigned to specific morphological aspects of pancreatic cystic lesions would improve the weight of EUS morphology. Palazzo *et al*[95] underlines this concept, proposing the creation of an international expert educational image bank for CPLs that could help to standardize image analysis. However, there are some studies that have clearly shown that EUS shows clearer images of some cystic aspects, such as diffuse or localized microcystic aspects, lobulated contours for serous cystoadenomas, debris for pseudocysts, connections with the pancreatic duct, grape-like, finger- or clubber-like aspects for IPMNs, and rounded contour and internal septa for MCN. Moreover, some EUS aspects, such as intracystic nodules, pericystic solid mass, localized thickening of the parietal wall or of the intracystic septa, and dilation of the pancreatic duct, are

Table 4 Accurancy of endoscopic ultrasound morphology in differentiating pancreatic cystic lesions (printed with permission of Dr M. Raimondi

Author	No. of patients	Study design	Accuracy (%)
Koito *et al*[57]	52	Retrospective	94
Cellier *et al*[64]	21	Retrospective	76
Pais *et al*[54]	51	Retrospective	86
Ahmad *et al*[60]	38	Retrospective	66
Sedlack *et al*[42]	34	Retrospective	82
Hernandez *et al*[58]	9	Retrospective	89
Frossard *et al*[59]	67	Retrospective	73
Brugge *et al*[61]	112	Prospective	51
Gerke *et al*[62]	66	Retrospective	67
Total	450		Median 72.5 (mean 77)

predictive of malignancy and some of these aspects are frequently better seen with EUS.

Analyses of data from nine studies[42,54,57-62,64] (Table 4), with a total of 450 patients, of accuracy of EUS morphology in differentiating CPLs showed a median of 72.5% (mean 77%). This is better than the 50%-60% accuracy of radiology[33-35] and slight different from the accuracy of CEA (79%)[61]. Compared with cytology, the accuracy of EUS morphology varies a great deal because of the significant heterogeneity in the results of the cytology studies, with an accuracy ranging between 51% and 93%[73] but with a median of 73%, which is quite close to the accuracy of EUS morphology. Moreover, EUS allows for the execution of FNA for cytological examination and intracystic fluid analysis, especially in such doubtful lesions as unilocular cystic pancreatic lesions, which do not have specific EUS aspects (Figure 5).

In general, cytology in every study showed low sensitivity and high specificity, allowing, when positive, to predict the type of lesion. CEA showed good accuracy for mucinous lesions when the cut-off was 192 ng/mL and a high specificity for serous cystoadenomas when using the low cut-off of 5 ng/mL. Amylase levels are undoubtedly useful for excluding pseudocyst. There are other diagnostic tests beyond intracystic fluid that are very promising, such as molecular analysis, variants of mucins, proteomic analysis and mRNA analysis, although larger studies than those done to date are needed for validation.

Several case reports and case series have shown the utility of EUS-FNA in diagnosing much rarer PCLs, such as cystic change of pancreatic neuroendocrine tumors[96], solid papillary neoplasm[97], lymphoepithelial cyst[98], pancreatic schwannoma[99] and pancreatic cystic lymphangioma[100].

We can conclude by saying that diagnosis of pancreatic cystic lesions is composed of different bits of information, derived from a number of different sources. EUS morphology and EUS-FNA are important diagnostic tools and can useful in solving this difficult diagnostic puzzle.

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BRIEF ARTICLE

Sedation practices for routine diagnostic upper gastrointestinal endoscopy in Nigeria

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Abstract

AIM: To determine the sedation practices and preferences of Nigerian endoscopists for routine diagnostic upper gastrointestinal endoscopy.

METHODS: A structured questionnaire containing questions related to sedation practices and safety procedures was administered to Nigerian gastrointestinal endoscopists at the 2011 annual conference of the Society for Gastroenterology and Hepatology in Nigeria which was held at Ibadan, June 23-35, 2011.

RESULTS: Of 35 endoscopists who responded, 17 (48.6%) used sedation for less than 25% of procedures, while 14 (40.0%) used sedation for more than 75% of upper gastrointestinal endoscopies. The majority of respondents (22/35 or 62.9%) had less than 5 years experience in gastrointestinal endoscopy. The sedative of choice was benzodiazepine alone in the majority of respondents (85.7%). Opioid use (alone or in combination with benzodiazepines) was reported by only 5 respondents (14.3%). None of the respondents had had any experience with propofol. Non-anaesthesiologist-directed sedation was practiced by 91.4% of endoscopists. Monitoring of oxygen saturation during sedation was practiced by only 57.1% of respondents. Over half of the respondents (18/35 or 51.4%) never used supplemental oxygen for diagnostic upper gastrointestinal endoscopy.

CONCLUSION: Sedation for routine diagnostic upper gastrointestinal endoscopy in Nigeria is characterized by lack of guidelines, and differs markedly from that in developed countries.

Key words: Gastrointestinal endoscopy; Nigeria; Sedation

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INTRODUCTION

Routine diagnostic upper gastrointestinal (GI) endoscopy is the standard practice for diagnosing esophageal, gastric and duodenal diseases. It has very low complication and mortality rates[1] and may be performed with or without sedation. The use of sedation improves the tolerance and acceptance of the examination[2], but increases the cost of the procedure and is responsible for about 50% of complications associated with the procedure[3].

Sedation practices differ from one country to anoth-

er and even vary within the same country. These differences may reflect many different factors, which include the personal differences and training of the endoscopist, the availability of anesthetic services, the need to train colleagues in endoscopic techniques, the cost and availability of monitoring equipment, differences in the availability and use of common drugs, and particularly, the expectations of the patient[4]. In the United Kingdom and United States, sedation is widely used in endoscopies. In France, 80% of colonoscopies are performed under general anesthesia, while in Germany and Finland most examinations are conducted without any form of anesthesia[4].

Unsedated upper GI endoscopy is effective in selected patients, but causes reduced operator satisfaction. A meta-analysis showed that sedation achieved better patient cooperation and satisfaction and a willingness to have it repeated[5].

Successful endoscopic procedures can be achieved with patients in either moderate or deep sedation or general anesthesia; however, moderate sedation is generally considered adequate to control the pain and anxiety of routine endoscopic examinations and to achieve adequate amnesia[6].

Sedation is a continuum of progressive impairment of consciousness ranging from minimal sedation to general anesthesia. Although clinicians may target a specific level of sedation, it is not always possible to predict how each patient will respond to sedative or analgesic medications. Patients can move in a fluid manner between these extremes[7]. Targeting moderate sedation is the goal, but in clinical practice some patients will transiently be in lighter or deeper levels of sedation. Targeting conscious levels results in an overall safer profile than targeting deeper levels and should result in a substantial safety margin for non-anesthesiologists.

Since the 1980s, the use of benzodiazepines, often in combination with an analgesic has become standard practice in the United States and many parts of Europe[8,9]. Time consuming and technically complex endoscopies of the GI tract such as endoscopic retrograde cholangio-pancreatography and endoscopic ultrasonography require deep sedation and propofol is a popular choice for induction and maintenance of deep sedation[10]. Propofol has also been adjudged a very safe sedative for endoscopist-directed sedation[11].

In Nigeria, there are currently no guidelines for sedation in GI endoscopy. This study was carried out to determine the sedation practices of Nigerian endoscopists for routine diagnostic upper GI endoscopy. Information obtained from this study would be useful not only in the audit of the practice of gastroenterology in a resource-poor setting such as Nigeria, but also in formulating guidelines and further research.

MATERIALS AND METHODS

In this study, a structured questionnaire was administered to all GI endoscopists who attended the annual scientific conference and general meeting of the Society for Gastroenterology and Hepatology in Nigeria (SOGHIN) which was held in Ibadan, Oyo State, Nigeria between June 23 and 25, 2011.

The questionnaire included 12 multiple choice questions focusing on the practices of routine diagnostic upper GI endoscopy. Such practices included sedation preference and administration, sedative drugs used, monitoring during sedation, use of supplemental oxygen, use of antispasmodic drugs and use of patient consent form. The data were expressed as percentages. Where appropriate, the difference between proportions was determined using χ^2. P value of < 0.05 was considered statistically significant.

RESULTS

Of 41 questionnaires handed out, 35 were completed and returned, giving a response rate of 85.4%. There were 31 males (88.6%) and 4 females (11.4%). The majority of endoscopists were physicians (82.9% or 29/35), while 14.3% (5/35) were surgeons. One respondent did not indicate whether he was a physician or a surgeon (2.8%).

Twenty two respondents (62.9%) had less than 5 years experience in GI endoscopy, while only 4 (11.4%) had up to 15 years experience (Table 1). Seventeen respondents (48.6%) performed less than 25% of routine diagnostic upper GI endoscopies with sedation, while 14 (40.0%) performed 75% or more of the procedures with sedation (Table 2). The difference between the proportions was not statistically significant ($\chi^2 = 0.2014$, $P = 0.6536$). With regard to the criteria for deciding who receives sedation (Table 3), 24 respondents (71.4%) used sedation for uncooperative patients, 14 (40%) for children, 9 (25.7%) for patients who requested it, and 12 (34.3%) for patients less than 60 years of age.

Regarding the question "Do you routinely ask for the preference of your patient for sedated or unsedated examination", 27 (77%) responded in the negative. Thirty endoscopists (85.7%) used benzodiazepine alone as the sedative drug. Only 5 respondents (14.3%) had used opioids alone or in combination with benzodiazepines. None of the respondents reported ever using propofol (Table 4).

Concerning the administration of the sedative; 20 endoscopists (57.1%) administered it themselves while 14 (40%) employed other non-anesthesiologist staff. Only 3 endoscopists (8.6%) answered that anesthesiologists administered the sedation (Table 5). Bolus administration was practiced by 26 endoscopists (74.3%), while only 9 (25.7%) administered it in titrated fashion. For sedated patients, 30 respondents (85.7%) monitored vital signs. However, 18 respondents (51.4%) monitored unsedated patients. Oxygen saturation and electrocardiogram (ECG) were monitored by only 20 respondents (57.1%) and 5 respondents (14.3%), respectively. Eighteen respondents (51.4%) never used supplemental oxygen

Table 1 Distribution of gastrointestinal endoscopists according to years of experience

Years of practice	No. of endoscopists (n = 35)	Percentage
< 5 yr	22	62.9
5 yr to 10 yr	3	8.5
> 10 yr to 15 yr	5	14.3
> 15 yr	4	11.4
Not stated	1	2.9
Total	35	100

Table 2 Frequency of using sedation in upper gastrointestinal endoscopy

Upper gastrointestinal endoscopies with sedation	No. of endoscopists (n = 35)	Percentage
< 25%	17	48.6
25%-49%	0	0
50%-74%	4	11.4
⩾ 75%	14	40.0
Total	35	100

(Table 6).

With regard to use of antispasmodics, the responses were always, in most cases, occasionally and never by 9 (25.7%), 3 (14.3%), 17 (48.6%) and 4 (11.4%) respondents, respectively. Informed consent prior to endoscopic examination was routinely obtained by 29 respondents (82.9%), while 6 (17.1%) did not obtain informed consent.

DISCUSSION

The practice of endoscopic sedation varies from country to country due to social, cultural, economic and regulatory influences[2-4,6]. Although the medical literature is replete with guidelines and recommendations for the practice of sedation in developed nations, principally the United States and Western Europe[12-15], minimal data exist about sedation practices in resource-poor countries including Nigeria. In this study, the questionnaire was administered directly to the endoscopists rather than studying one or two individuals adjudged to be experts in the field and accepting their views as representative of whole nations[16]. The problem with the latter approach is that responses to questions could reflect preconceived beliefs about practice patterns internationally rather than actual practice.

The response rate in this study was 85.4%. This is considered satisfactory for a study of this nature. There were only 35 respondents. This clearly reflects a doctor to population ratio of 3 per 10 000 in Nigeria, compared to US which stands at 26 per 10 000. The gap is even wider when one considers the gastroenterologist to population ratio. Nigeria has a population of over 150 million[17] but has less than 60 gastroenterologists (registered with the national society, SOGHIN). Of these gastroenterologists, close to a third do not practice GI endoscopy because they work in centres where facilities for endoscopy do not exist. Therefore the 35 endoscopists who responded to the questionnaire are representative of the total number on the ground.

Table 3 Reasons for using sedation

Reason	No. of endoscopists (n = 35)	Percentage
Uncooperative patients	24	71.4
Children	14	40
Patients < 60 yr	12	34.3
Patient's request	9	25.7
Patients > 60 yr	5	14.3

Table 4 Frequency of use of different sedative drugs

Drug(s)	No. of endoscopists (n = 35)	Percentage
Benzodiazepine alone	30	85.7
Opioid alone	1	2.9
Benzodiazepine + opioid	4	11.4
Propofol	0	0
Total	35	100

The majority of the GI endoscopists in Nigeria are physicians (82.8%). This is because in most training institutions it was the physicians that first introduced endoscopy into their practice in the early 1980s. In recent times, more surgeons have become interested and are making efforts to be trained.

In this study, the majority of respondents had less than five years practice experience in GI endoscopy. This again reflects the fact that endoscopy practice in Nigeria is still at a very early stage of development[18]. Some of the pioneer endoscopists were lost to the brain drain in the 1980s and 1990s[19,20], with the result that the training of future endoscopists suffered a tremendous setback. Most of the practicing gastroenterologists in Nigeria are products of the two postgraduate medical colleges (West African College of Physicians/Surgeons and the National Postgraduate Medical College of Nigeria).

With regard to use of sedation for routine upper GI endoscopy, 48.6% use sedation in less than 25% of procedures, while 40% use sedation in more than 75% of procedures (P = 0.6536). This means that among Nigerian digestive endoscopists, sedated and unsedated procedures are practiced. The use of sedation is said to be on the increase in some developed societies[12]. However, the present study is unable to make any inference in that regard as this is the first study in Nigeria on this subject.

The majority of respondents (77%) did not give patients the privilege of choosing between sedated and unsedated procedures. This is not right as medical practice has moved sharply from the traditional paternalistic fashion to a model where patients actually participate in taking decisions regarding their care[21]. With regard to the reasons for using sedation in some patients and not others, 71.4% answered that they sedate patients who are uncooperative. This suggests that such sedation

Table 5 Personnel responsible for administering sedation

Personnel	No. of endoscopists (n = 35)	Percentage
Endoscopist	20	57.1
Nurse	7	20.0
Doctor (resident doctors, medical officers, house officers)	7	20.0
Anesthesiologist	3	8.6

Table 6 Frequency of use of supplemental oxygen

Type of patient	No. of endoscopists (n = 35)	Percentage
None	18	51.4
High risk patients	9	25.7
Oxygen desaturation	8	22.9
All	0	0
No response	1	2.9

may only be administered after the procedure has commenced and the patient is judged to be uncooperative. The decision to sedate is supposed to precede the actual procedure and must be based on evidence.

Benzodiazepine alone is employed by most respondents (85.7%), while only 14.3% use opioids either alone or in combination with a benzodiazepine. Patients undergoing GI endoscopy may be anxious, as the procedure may be uncomfortable or painful. Effective sedation throughout the procedure is an important aspect of patient management and it should meet the anxiolytic and analgesic needs of the individual patient[22]. The fact that most Nigerian endoscopists use benzodiazepine alone means that the concept of balanced sedation is not observed and many patients may actually be undersedated. Granted that both the pharmacological effects and the side effects of benzodiazepines and opioids are synergistic and must be used with caution[23], observations from Western Europe[12,13] and the United States[24] indicate that a benzodiazepine/opioid combination is the preferred method of endoscopic sedation worldwide. The 2 drug classes have a long history of safety, efficacy and widespread acceptance by non-anesthesiologists[25]. They also have pharmacological antagonists which is an added advantage.

None of the respondents had any experience with propofol. The use of this sedative has been expanding in most developed countries of the world. It has a good safety profile[11]. However, its use is highly regulated in America and Europe[26,27]. The observed low rate of opioid use and non-use of propofol for routine diagnostic upper GI endoscopy in this study may be partly explained by the physician-dominated digestive endoscopy. Traditionally, surgeons work with anesthesiologists and anesthesiology is part of the standard training of surgeons. It is therefore likely that an endoscopy service that is dominated by surgeons may employ opioids and propofol more than that observed in this study.

Bolus rather than titrated injection is practiced by 74.3% of respondents. Although clinicians may target a specific level of sedation, it is not always possible to predict how each patient will respond to sedative or analgesic medications. Clinicians commencing sedation/analgesia intending to produce a given level of sedation should be able to rescue patients whose level of sedation has become deeper than initially intended. A key principle in the administration of sedation is to titrate medications in incremental doses to the desired sedative effect[28]. Sedatives and analgesics must be titrated based upon the condition of the patient, information from monitoring equipment and the needs of a procedure[15].

The person who administers the sedation may be an anesthesiologist or a non-anesthesiologist. In this study, the sedation is administered by a non-anesthesiologist in 97% of respondents. It is common knowledge that the endoscopists, nurses and other doctors who administer these sedatives have not received any formal training for that purpose. There is uniform agreement in the literature and all relevant societal guidelines agree that specific training is needed for both the endoscopic procedure and any sedation associated with that procedure[26,28-32]. Some even specify a certain number of supervised procedures required before competency can be assessed[32]. The time has come for similar guidelines to be developed for resource-poor countries including Nigeria.

With regard to monitoring, 85.7% of respondents monitor sedated patients with vital sign measurements. Oxygen saturation and ECG are monitored by 57.1% and 14.3% of respondents, respectively. This is clearly unsatisfactory. Since sedation occurs along a continuum, all sedated patients should have their level of consciousness determined periodically during the examination and recovery periods using a standardized sedation scale. The risk of an unplanned cardiopulmonary event is directly related to the level of sedation. As the depth of sedation increases, so too does the likelihood that a patient will develop loss of the airway reflex, hypoventilation and/or apnea, or cardiovascular instability[15]. Direct observation of a patient's ventilation and airway status by a trained individual may detect potential problems prior to any automated monitoring device. Monitoring of the patient's heart rate, arterial oxygen saturation, and blood pressure must be performed in patients receiving sedation. This recommendation is common to several societal guidelines[15,26]. The American Society of Anesthesiologists guidelines recommend continuous monitoring of patients with significant cardiovascular disease or arrhythmia during moderate sedation. For Nigeria, a home-grown guideline will be able to address these issues taking cognizance of the personnel and resources available.

Over half of the respondents (51.4%) said they never used supplemental oxygen. Less than half of the respondents admitted using supplemental oxygen for specific indications. This is at variance with what occurs in many developed countries. Supplemental oxygen improves oxygenation and in the event of hypoventilation or apnea, extends the time that a patient remains adequately

oxygenated. It has become standard practice throughout many areas of the world to administer supplemental oxygen during endoscopy to all patients receiving moderate sedation[15,30,33,34]. The low rate of administration of supplemental oxygen among Nigerian endoscopists may be related to the low rate of utilization of moderate/deep sedation as well as non availability of oxygen in the endoscopy suites.

The majority of respondents (82.9%) said they routinely obtained informed consent from patients prior to sedation. That is good clinical practice. However, 17.1% did not obtain consent. The concept of informed consent is a process that must take place between physician and patient, prior to the procedure or treatment, and should include discussion of pertinent risks, benefits and alternatives[2,35,36]. Besides, properly informed patients seldom sue. Busy endoscopy units and long waiting lists for gastroscopy are not an excuse for omitting proper patient information[37,38] and not asking their preference for sedation.

Over a quarter of the respondents used antispasmodic injection (hyoscine) in all diagnostic upper GI endoscopies. This is a very important finding because the role of antispasmodic agents in GI endoscopy remains controversial[39]. There are fears about anticholinergics initiating glaucoma. There is also an unproven suspicion that the stomach is rendered atonic and more difficult to distend with air thereby making the procedure more difficult and heightening the risk of perforation. There have also been reports of adverse reactions to hyscine[40-42]. Recommendations based on evidence are needed in this area of upper GI endoscopy.

In conclusion, the sedation practices of Nigerian GI endoscopists for routine upper GI endoscopy differ significantly from what is recommended by many national professional societies in the developed world. There is also considerable disparity between the sedation practices of different endoscopists. This state of affairs has been brought about by a complete absence of guidelines for sedation practices in Nigeria. There is therefore an urgent need for all the stakeholders, particularly gastroenterologists and anesthesiologists, to come up with guidelines appropriate to the existing human and material resources.

COMMENTS

Background

Endoscopy is standard procedure for the diagnosis and treatment of diseases of the gastrointestinal tract. Sedation improves patient tolerance and compliance for the procedure and also improves the quality of an endoscopic examination. The use of sedation is high in North America and Australia, but varies considerably in Europe, Asia and Africa. This study sought to determine the sedation preferences and practices of gastrointestinal endoscopists in Nigeria, a typical resource-limited African country.

Research frontiers

Nigeria is the most populous black country in the world with a population of over 160 million, but gastrointestinal endoscopy is still at a very rudimentary stage of development. The aim of this study was to determine the sedation practices of endoscopists for routine diagnostic upper gastrointestinal endoscopy using a questionnaire which was administered to all Nigerian gastrointestinal endoscopists who attended their annual conference. In this way, the actual practitioners were reached rather than studying a few individuals and using their views, perceptions and preferences to make generalizations.

Innovations and breakthroughs

Both sedated and unsedated upper gastrointestinal endoscopy were common as 48.6% used sedation for less than 25% of procedures, while 40.0% used sedation in more than 75% of endoscopies. The most commonly used sedative is benzodiazepine (85.7%), while opioid use is limited to 14.3%. None of the endoscopists had any experience with propofol. Other findings were lack of guidelines, lack of proper monitoring of sedated patients and lack of non-anesthesiologist staff trained in the use of propofol.

Applications

The results from this study would provide the necessary framework for the eventual development of a guideline for sedation in gastrointestinal endoscopy in Nigeria. Similarly, the training and retraining needs of practicing endoscopists would be better addressed.

Terminology

Endoscopy means looking inside and gastrointestinal endoscopy means looking inside the gastrointestinal tract using an instrument called an endoscope. Because the procedure is uncomfortable and may actually be painful, the standard practice is to carry out the procedure with sedation. Sedation is the reduction of irritability or agitation by administration of a drug (sedative).

Peer review

This is an interesting survey of sedation practice for upper gastrointestinal endoscopy in Nigeria. Clearly sedation practice varies between countries and it is important to develop local guidelines and safety standards, and this survey would be an important first step in this direction. The paper is generally well written.

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CASE REPORT

Unusual penetration of plastic biliary stent in a large ampullary carcinoma: A case report

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Abstract

Endoscopic biliary stenting is a well-established treatment of choice for many obstructive biliary disorders. Commonly used plastic endoprostheses have a higher risk of clogging and dislocation. Distal stent migration is an infrequent complication. Duodenum is the most common site of a migrated biliary stent. Intestinal perforation can occur during the initial insertion or endoscopic or percutaneous manipulation, or as a late consequence of stent placement. A 52-year-old male who presented with obstructive jaundice underwent endoscopic retrograde cholangiopancreatography (ERCP) with plastic stent placement. However, jaundice did not improve and he then underwent ERCP which revealed the plastic stent penetrating the ampullary tumor into the duodenal wall causing malfunction of the stent. A new plastic stent was inserted and the patient underwent Whipple's operation. He is currently doing well after the operation.

Key words: Complication; Endoscopic retrograde cholangiopancreatography; Penetration; Perforation

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INTRODUCTION

Over the last two decades; after reporting the first use of a plastic stent in 1980 for a malignant biliary obstruction of the distal common bile duct[1], endoscopic biliary drainage is now a well-established treatment of choice for many biliary disorders. Today, a variety of plastic stents of different shapes, sizes and length are available in the market[2,3]. Commonly used plastic endoprostheses are less expensive, but have a higher risk of clogging and dislocation[4].

The main problem with plastic stents is stent malfunction leading to recurrent jaundice and cholangitis after weeks or months requiring stent exchange in 30% to 60% of patients[5]. To avoid stent migration, the biliary stent should be placed across the sphincter of Oddi[6]. Distal stent migration is an infrequent late complication, but occurs in up to 6% of cases[7,8]. The majority of stents pass through the intestinal system without any problems. However, if the stent gets stuck in the bowel then it should be removed; endoscopic retrieval is often possible and surgical intervention is rarely necessary[9,10]. The duodenum is the most common site of a migrated

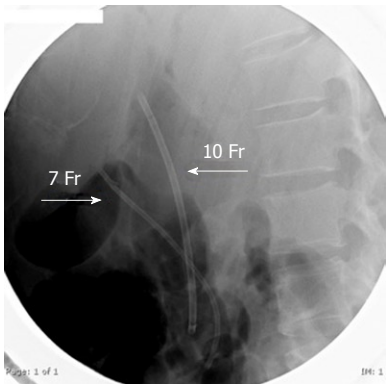

Figure 1 Fluoroscopic image after placement of a new 10 Fr plastic stent in the common bile duct with the previous 7 Fr plastic stent penetrating the duodenum.

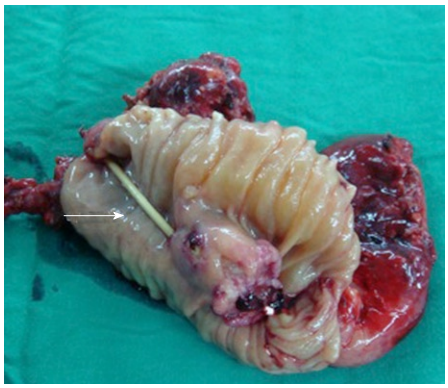

Figure 2 Operative specimen (Whipple's operation) showed the plastic stent was not inside the common bile duct (white arrow). It penetrated the ampullary mass into the duodenum.

biliary stent[11-14]. However, complications such as perforations and fistulisations in the rest of the small intestine[15] and colon are also seen.

In the recent literature, most (92%) cases of intestinal perforation were in the duodenum after endoscopic or percutaneous placement of a biliary stent[16-19]. These were due to various mechanisms; firstly, the stent may have been placed incorrectly, and the mechanical force exerted by the tip of the plastic stent against the duodenal mucosa can lead to necrosis of the wall over time. Secondly, inflexibility or a stent of incorrect length may lead to pressure necrosis[20,21].

CASE REPORT

We report here on a 52-year-old male who presented with fever and jaundice. His liver function tests were TB/DB: 7.3/6.2, Albumin/Globulin: 3.6/3.6, SGOT/SGPT: 119/214, Alkaline phosphatase: 621. An abdominal computed tomography scan showed marked dilatation of the common bile duct (CBD) with gallstone. He underwent endoscopic retrograde cholangiopancreatography (ERCP) which revealed a large ulceroproliferative mass at the ampulla. A plastic stent (7 Fr. 10 cm: Amsterdam type) was placed over the guidewire. Multiple biopsies were performed at the ampulla and histopathological results showed adenocarcinoma. Two weeks later, his jaundice had not improved. ERCP was performed again. After the duodenal scope was introduced, penetration of the previous stent in the ampullary mass into the duodenal lumen was seen. Cannulation of the CBD through the ampulla opening where the tip of the previous plastic stent was found was attempted, but failed. Precut sphincterotomy using a needle knife at the duodenal wall (fistulotomy technique) was performed. Finally the guidewire could be passed into the CBD over the sphincterotome catheter. A new plastic stent (10 Fr. 10 cm: Amsterdam type) was placed into the CBD (Figure 1). Good run off of infected bile and contrast media was seen. One month later, the patient underwent Robotic-assisted Whipple's operation (Figure 2). There were no post-operative complications. He was discharged from the hospital two weeks after surgery. He is currently doing well.

DISCUSSION

Plastic stent occlusion due to tumor overgrowth or bile clogging the lumen is the most common (54%) problem seen with endoprostheses following ERCP[18]. Although it is seen in about 6% of cases; migration of the stent is one of the most important problems[2,7]. When distal migration occurs, the majority of stents pass through the intestinal system without any problem. However, if a stent gets stuck in the bowel then it should be removed. Generally, removal is done endoscopically and surgical intervention is rarely necessary[8,9].

Intestinal perforation can occur during initial insertion, manipulation or as a late consequence of biliary stent placement. In the recent literature, most cases of intestinal perforation (92%) were in the duodenum after endoscopic or percutaneous placement of a biliary stent[4,15-17]. The incidence of small bowel perforation following ERCP is 0.08%-0.57%[19,20]. In 1999, Howard *et al*[21] classified perforations after ERCP into 3 groups; guidewire-related, periampullary- or postsphincterotomy-related and scope-induced perforations in which periampullary-related were the most common. In 2000, Stapfer *et al*[22] classified ERCP-related perforations, in descending order of severity, into four types: Type Ⅰ: lateral or medial wall duodenal perforation, Type Ⅱ: peri-Vaterian injuries, Type Ⅲ: distal bile duct injuries related to wire/basket instrumentation and Type Ⅳ: retroperitoneal air alone.

In our patient, following insertion of the first plastic stent into the CBD there was lateral penetration of the stent just proximal to the ampulla; which was due, in our opinion, to the tumor mass effect on the stent pushing it into the second part of the duodenum. During the second ERCP after accessing the first portion of the duodenum we noted the previous stent, and thought that distal migration had occurred. When we proceeded

towards the ampulla we observed the distal part of the stent coming out of the ampulla. We failed to cannulate the CBD using a standard technique. Therefore, using the precut fistulotomy technique a new 10 Fr. plastic stent was placed and good bile flow was observed. In this case report we wanted to share this atypical complication of ERCP and plastic stent placement.

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World J Gastrointest Endosc 2012 June 16; 4(6): I
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Events Calendar 2012

January 19-21, 2012
American Society of Clinical Oncology 2012 Gastrointestinal Cancers Symposium
San Francisco, CA 3000, United States

January 19-21, 2012
2012 Gastrointestinal Cancers Symposium
San Francisco, CA 94103, United States

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

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

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

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

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

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

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

March 31-April 1, 2012
5th Annual Endoscopy Directors Meeting Endoscopy Unit Management in the 21st Century: Issues, Solutions, and Plans for the Future
Washington, DC 20057, United States

April 8-10, 2012
9th International Symposium on Functional GI Disorders
Milwaukee, WI 53202, United States

April 15-17, 2012
European Multidisciplinary Colorectal Cancer Congress 2012
Prague, Czech

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

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

April 22-24, 2012
EUROSON 2012 EFSUMB Annual Meeting
Madrid, Spain

April 28, 2012
Issues in Pediatric Oncology
Kiev, Ukraine

May 3-5, 2012
9th Congress of The Jordanian Society of Gastroenterology
Amman, Jordan

May 7-10, 2012
Digestive Diseases Week
Chicago, IL 60601, United States

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

May 18-23, 2012
SGNA: Society of Gastroenterology Nurses and Associates Annual Course
Phoenix, AZ 85001, United States

May 19-22, 2012
2012-Digestive Disease Week
San Diego, CA 92121, United States

June 18-21, 2012
Pancreatic Cancer: Progress and Challenges
Lake Tahoe, NV 89101, United States

September 8-9, 2012
New Advances in Inflammatory Bowel Disease
La Jolla, CA 92093, United States

September 8-9, 2012
Florida Gastroenterologic Society 2012 Annual Meeting
Boca Raton, FL 33498, United States

September 15-16, 2012
Current Problems of Gastroenterology and Abdominal Surgery
Kiev, Ukraine

October 4-6, 2012
EURO-NOTES 2012: NOTES and Advanced Interventional Endoscopy
Prague, Czech Republic

October 19-24, 2012
American College of Gastroenterology 77th Annual Scientific Meeting and Postgraduate Course
Las Vegas, NV 89085, United States

November 3-4, 2012
Modern Technologies in Diagnosis and Treatment of Gastroenterological Patients
Dnepropetrovsk, Ukraine

December 1-4, 2012
Advances in Inflammatory Bowel Diseases
Hollywood, FL 33028, United States

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GENERAL INFORMATION

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253), is a monthly, open-access (OA), peer-reviewed online journal supported by an editorial board of 400 experts in gastrointestinal endoscopy from 45 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results.

Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJGE* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJGE* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJGE* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

Aims and scope

The major task of *WJGE* is to report rapidly the most recent results in basic and clinical research on gastrointestinal endoscopy including: gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy. Papers on advances and application of endoscopy-associated techniques, such as endoscopic ultrasonography, endoscopic retrograde cholangiopancreatography, endoscopic submucosal dissection and endoscopic balloon dilation are also welcome.

Columns

The columns in the issues of *WJGE* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in gastrointestinal endoscopy; (9) Brief Article: To briefly report the novel and innovative findings in gastrointestinal endoscopy; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJGE*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of gastrointestinal endoscopy; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in gastrointestinal endoscopy.

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Statisital review is performed after peer review. We invite an expert in Biomedical Statistics from to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

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In the interests of transparency and to help reviewers assess any potential bias, *WJGE* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent
Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights
When reporting the results from experiments, authors should follow the highest standards and the trial should comform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

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Title: Title should be less than 12 words.

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Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

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There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

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Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles, rapid communication and case reports, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1948-5190/g_info_20100316080002.htm.

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Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

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Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

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Data that are not statistically significant should not be noted. [a]$P <$

0.05, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of P values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of P values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

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When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

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Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

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Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

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

In press

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

Organization as author

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

Both personal authors and an organization as author

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

No author given

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

Volume with supplement

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

Issue with no volume

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

No volume or issue

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

Books

Personal author(s)

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

Chapter in a book (list all authors)

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

Author(s) and editor(s)

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

Conference proceedings

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

Conference paper

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

Electronic journal (list all authors)

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

Patent (list all authors)

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

Statistical data
Write as mean ± SD or mean ± SE.

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

Units
Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/wjg/help/15.doc.

Abbreviations
Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics
Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

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