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EDITORIAL

Endoanal ultrasonography in fecal incontinence: Current and future perspectives

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Abstract

Fecal incontinence has a profound impact in a patient's life, impairing quality of life and carrying a substantial economic burden due to health costs. It is an underdiagnosed condition because many affected patients are reluctant to report it and also clinicians are usually not alert to it. Patient evaluation with a detailed clinical history and examination is very important to indicate the type of injury that is present. Endoanal ultrasonography is currently the gold standard for sphincter evaluation in fecal incontinence and is a simple, well-tolerated and non-expensive technique. Most studies revealed 100% sensitivity in identifying sphincter defect. It is better than endoanal magnetic resonance imaging for internal anal sphincter defects, equivalent for the diagnosis of external anal sphincter defects, but with a lower capacity for assessment of atrophy of this sphincter. The most common cause of fecal incontinence is anal sphincter injury related to obstetric trauma. Only a small percentage of women are diagnosed with sphincter tears immediately after vaginal delivery, but endoanal ultrasonography shows that one third of these women have occult sphincter defects. Furthermore, in patients submitted to primary repair of these tears, ultrasound revealed a high frequency of persistent sphincter defects after surgery. Three-dimensional endoanal ultrasonography is currently largely used and accepted for sphincter evaluation in fecal incontinence, improving diagnostic accuracy and our knowledge of physiologic and pathological sphincters alterations. Conversely, there is currently no evidence to support the use of elastography in fecal incontinence evaluation.

Key words: Endoanal ultrasonography; Fecal incontinence; External anal sphincter; Internal anal sphincter; Obstetric anal sphincter injuries; Three-dimensional endoanal ultrasonography; Elastography

Core tip: Clinicians need to be more alert to fecal incontinence, which is a serious under-reported problem. Endoanal ultrasonography is currently the gold standard for sphincter evaluation in these patients. The most important cause of fecal incontinence is obstetric injury and the most relevant questions and controversies are related to this. The diagnosed of sphincter injury after delivery and after complete primary repair is much lower to that found by ultrasonography, and many

of these women developed fecal incontinence. The clinical evaluation, technical aspects, advantages and limitations and the current role of three dimensional ultrasonography and real-time elastography will also be discussed.

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FECAL INCONTINENCE: WHAT SHOULD WE KNOW BEFORE PERFORMING ENDOANAL ULTRASONOGRAPHY?

Fecal incontinence (FI) has a profound impact in a patient's personal life, impairing social interaction, professional and sexual activity and carries a substantial economic burden due to health costs.

The prevalence varies from 2.2% to 25 % in the community[1] and up to 50% of the nursing home residents[2]. Although a relevant problem, it is an underdiagnosed condition, since many affected patients are reluctant and embarrassed to report it. In a study by Sultan *et al*[3], none of the women that developed FI after vaginal delivery spontaneously reported their symptoms or sought medical attention. So, it is essential that health professionals, mainly those who look after women ask about symptoms of FI, especially in the postpartum period.

Loss of continence can result from several mechanisms, dysfunction of the anal sphincters, abnormal rectal compliance, decreased rectal sensation, altered stool consistency, or a combination of any of these abnormalities. FI is often multifactorial condition, may be the consequence of local, anatomical or systemic disorders, non-traumatic or traumatic lesions. Not every patient with sphincter injury develops incontinence, and, in addition, patients can have incontinence without sphincter injury. There are several women that only develop FI several years (20 or 30 decades) after delivery.

Patient evaluation should always include a detailed clinical history, inspection of the perianal area and a digital rectal examination. The type of incontinence (urge or passive), obstetric history (vaginal deliveries, use of forceps, perineal laceration), previous anorectal surgery, coexisting comorbidities, anal resting tone and squeeze pressure are fundamental to understand the mechanism behind the impairment and this information should never be neglected. Patients with urge incontinence often have weakness of the external anal sphincter (EAS) and reduced squeeze pressures or reduced rectal capacity with rectal hypersensitivity. Patients with passive FI, often have weakness of the internal anal sphincter (IAS) and lower resting pressure[4]. Taking all this information into consideration before endoanal ultrasonography (EAUS) is performed, can indicate the type of injury found.

There are several clinical scores that can be used to access severity, like the American Medical System, Pescatori score, Vaizey scale, Rockwood score or the Cleveland Clinic (Wexner) Incontinence Score[5]. These scores allow a more objective and reproducible assess of FI severity and a comparison of patients and treatments, namely the outcomes of both conservative and surgical treatments.

EAUS IN FECAL INCONTINENCE

EAUS is currently the gold standard technique for sphincter evaluation in FI[6]. The first studies in EAUS were performed by Law *et al*[7,8], in the early 1990s, comparing EAUS with electromyography, EAUS proved to be better tolerated and a useful technique for assessing defects of the anal sphincters. Most studies revealed 100% sensitivity in identifying sphincter defect. It is important to search for sphincter discontinuity, sphincter thinning and perform perineal body measurement. Discontinuity of the sphincter indicates a tear, and scarring is characterized by loss of the normal texture that usually has low reflectiveness. IAS tears appear normally as hyperechoic breaks and EAS tears appear as relatively hypoechoic areas (Figure 1). IAS thickness measurement in adults is abnormal if less than 2 mm (suggestive of degeneration) and generalized EAS atrophy is difficult to evaluate in EAUS. Perineal body measurement improves visualization of anterior sphincter lesions in females. A perineal body thickness of 10 mm or less is considered abnormal, whereas 10 mm to 12 mm is associated with sphincter defect in one-third of patients and those with 12 mm or more are unlikely to harbour a defect unless they previously have undergone reconstructive perineal surgery[9-11].

During the exam, the number, the circumferential extent (radial angle in degrees or in hours of the clock) and longitudinal extent (proximal, distal or full length) of the defect should be reported.

There are several possible pitfalls during EAUS that can simulate sphincter tears. A correct diagnose is important for FI assessment and for choosing the best therapeutic approach; a proper training in EAUS is fundamental. In many cases, it is not the endoscopic ultrasound practitioner that is performing the EAUS. These are two different techniques and specific training is needed for endoscopic ultrasound practitioners enrolled in EAUS.

Anal sphincteroplasty should be considered in patients with FI who do not respond to conservative therapy and who have an anatomic sphincter defect. Short-term outcomes suggest good-to-excellent results,

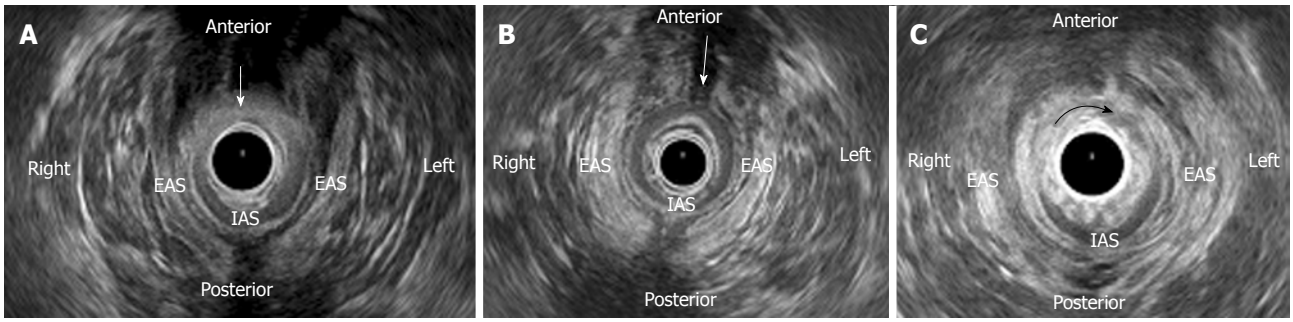

Figure 1 Endoanal ultrasound images of patients with fecal incontinence. A: A combined defect (arrow) of the external anal sphincter (EAS) from 10 to 2 o'clock and of the internal anal sphincter (IAS) from 9 to 3 o'clock positions, in a woman due to an obstetric anal sphincter injury; B: An anterior EAS defect (arrow), in a woman due to an obstetric anal sphincter injury; C: An IAS defect (arrow) from 8 to 4 o'clock position, in a man as a complication of a previous anorectal surgery (due to fistula).

but the benefits tend to deteriorate with long-term follow-up[4].

EAUS and endoanal magnetic resonance imaging (MRI) are comparable for the diagnosis of EAS defects, but IAS defects are less well assessed on MRI[12]. EAUS is simple, well-tolerated and non expensive. Endoanal MRI is expensive, not generally available, unsuitable in claustrophobic patients and those with metal implants. Endoanal MRI is superior to two-dimensional (2D) EAUS for identifying EAS atrophy. EAUS cannot distinguish fatty infiltration from normal muscle tissue and the boundaries of the EAS are harder to determine. Comparison between endoanal MRI and three-dimensional (3D) EAUS capacity for EAS atrophy evaluation revealed conflicting results. Cazemier *et al*[13] showed that both techniques are comparable in detecting EAS atrophy, although there is a substantial difference in grading. West *et al*[14] demonstrated that no 3D EAUS measurements are suitable parameters for assessing EAS atrophy. It is important to recognize atrophy because it is associated with a poor clinical outcome of sphincter repair.

EAUS and anorectal manometry are complementary investigations. EAUS allows anal sphincter morphology assessment and manometry anal sphincter function evaluation. Studies comparing both techniques show good correlation between them in partial or complete defects of the anal sphincter[15].

Most studies show poor agreement between digital anorectal examination and EAUS. In a study by Sultan *et al*[16] the clinical examination was only 50% accurate at predicting anal sphincter defects and Jeppson *et al*[17] show a specificity of 32% for digital anorectal examination in detecting anal sphincter defects seen on EAUS; however, Dobben *et al*[18] reported increased correlation between digital examination and EAUS based on size of the sphincter defect. Notwithstanding, performing digital anorectal examination is important in the evaluation of a patient with FI, helping to differentiate other potential causes such as tumor or fecal impaction.

It is important to ask patients about the presence of FI directly rather than relying on spontaneous reporting[4] and initial patient evaluation should include a detailed clinical history, inspection of the perianal area and a digital rectal examination. Manometry is important for anal sphincters function evaluation, anal sphincter resting and squeeze pressures are the key parameters[4]. EAUS is the gold standard for diagnosing anal sphincters tear and IAS degeneration. If EAS atrophy is suspected, endoanal MRI should be performed. Needle electromyography of the anal sphincter should be considered in patients with clinically suspected neurogenic sphincter weakness, particularly if there are features suggestive of proximal (*i.e.*, sacral root) involvement[4].

OBSTETRIC ANAL SPHINCTER INJURIES: A REAL PROBLEM

The most common cause of FI is anal sphincter injury related to vaginal delivery in female, due to direct anal sphincter laceration or indirect damage to sphincter innervation.

Two EAUS-based scoring systems have been proposed to define the severity of anal sphincter damage, both of them in women with obstetric anal sphincter injuries (OASIS). Starck *et al*[19] introduced a specific score, with 0 indicating no defect and 16 corresponding to a defect > 180° involving the whole length and depth of both sphincters. Norderval *et al*[20] reported a simplified system, including fewer categories and not recording partial defects of the IAS. The maximal score of 7 denotes defects in both the EAS and the IAS exceeding 90° in the axial plane and involving more than half of the length of each sphincter. Both scoring systems have demonstrated a good correlation between the extent of sphincter defects and the degree of FI. Scoring systems may help the clinician in choosing the appropriate treatment for patients with FI, but studies are needed.

Obstetric tears are divided into several subclasses, initially described by Sultan[21], and then adopted by the Royal College of Obstetricians and Gynaecologists (RCOG): injury to the perineal skin grade 1; injury to

the perineum involving the perineal muscles grade 2; involving the anal sphincter < 50% EAS grade 3a; > 50% EAS grade 3b; involvement of the IAS grade 3c; involvement of the anal sphincter as well as the anorectal epithelium grade 4[19]. OASIS encompasses both third- and fourth-degree perineal tears. They are identified in 0.6%-9.0% of vaginal deliveries where mediolateral episiotomy is performed, but the detection in EAUS is much higher[22].

A landmark study by Sultan *et al*[3] in 1993, using EAUS reported occult anal sphincter injury in 35% of women, six weeks after their first vaginal delivery. The incidence of *de novo* defects in multiparous females was 4.2%. The incidence of occult sphincter damage after vaginal delivery was unknown, previously to this study. Only 3% of primiparous women had an injury during delivery that was apparent in clinical examination. Results also suggested that the structural injury to the sphincters was permanent, since they were also present at 6 mo. Notably, only one third of women with sphincter defects in EAUS had FI.

In 2003, Oberwalder *et al*[23] published a meta-analysis of 717 vaginal deliveries (including the study by Sultan[21]) and found an incidence of occult sphincter damage of 26.9% in primiparous women and 8.5% of new defects in multiparous women. In one third of these women, postpartum sphincter damage was symptomatic.

Perhaps women with occult sphincter defect, but without FI can have sufficient residual sphincter function[21] or, since several mechanisms contribute to continence, they may compensate for this injury. The peak of incidence of FI is in the fifth and sixth decades of life in women, so the cumulative effect of deliveries, aging, menopause, progression of neuropathy may contribute for sphincter weakness in the long term and FI developing several years (20 or 30 decades) after delivery.

The clinical relevance of screening for occult anal sphincter laceration is controversial, mainly in asymptomatic defects. In a prospective cohort study by Frudinger *et al*[24], including primiparas with occult anal sphincter lacerations, at 10-year follow-up, only women who were symptomatic in the immediate postpartum period had deterioration over time of FI. Conversely, a randomized control trial by Faltin *et al*[25] showed that EAUS after childbirth improves the diagnosis of anal sphincter tears, and their immediate repair decreases the risk of severe FI. In this study, 752 primiparas with no clinically recognized anal sphincter laceration (occult) were assigned to undergo or not an EAUS immediately after delivery and diagnosed lacerations were repaired. In the EAUS group significantly fewer women reported severe FI at 3 and 12 mo compared to those who did not undergo EAUS. Using these data, it was estimated that 29 women would have to undergo EAUS to prevent one case of severe FI.

The current guidelines of the RCOG from 2007[22] state that "As there are clear difficulties with availability, access to staff trained in EAUS on the labour ward, image quality and patient acceptability, the use of EAUS in detecting anal sphincter injury immediately after delivery should be viewed as a research tool at present". There is no recommendation about screening women later after vaginal delivery for occult sphincter defects. Thus, data are controversial for asymptomatic patients. There are no cost-benefit studies of EAUS in this setting, or whether asymptomatic patients could benefit from it. Currently, the major investment should be in improving the identification of OASIS immediately after delivery. It is unclear, if occult sphincter defects are missed tears or true "occult" defects; probably the vast majority are not diagnosed clinically at time of delivery.

If an OASIS is identified immediately after vaginal delivery, it should be repaired. The RCOG[22] recommend that for repair of the external anal sphincter, either an overlapping or end-to-end (approximation) method can be used; if the IAS is identified, it is advisable to repair separately with interrupted sutures. Repair should be conducted in an operating theatre, under regional or general anaesthesia, by appropriately trained practitioners. Although primary reconstruction of the sphincters, more than 50% of women experience some change in continence (mainly to flatus) and the effect deteriorates with time[26]. Having a persistent sonographic defect after primary repair of OASIS has been shown to be associated with ongoing incontinence symptoms[27,28]. Studies show a high frequency of endosonographic sphincter defects after primary repairs, between 54% and 93% of women[29-32]. In a study using EAUS performed 2-7 d after delivery in women who had undergone a primary repair of an OASIS, 90% had endosonographic sphincter defects. In this study the extent of the endosonographic defects were mainly determined by the surgical experience of the doctor performing the repair, and not by the clinical degree of the tear[19].

The current guidelines of the RCOG[22] also do not make recommendations about using EAUS for confirming a complete primary repair. According to these guidelines "If a woman is experiencing incontinence or pain at follow-up, referral to EAUS and anorectal manometry should be considered". Considering the very high rate of sphincter defects detected by EAUS after primary repair, the high percentage of women that have some continence alteration and the difficulty in assessing the complete reparation of defects immediately after delivery, is EAUS confined to symptomatic women enough? In 2006, Starck *et al*[32] conducted a prospective study that included women who had suffered an OASIS at delivery and underwent EAUS at 1 wk, 3 mo and 1 year after primary suture. There was a positive correlation between the endosonographic sphincter defect score at 1 wk, 3 mo and 1 year and the Wexner incontinence score at 1 and 4 years. Endosonographic sphincter defect score at 1 wk was the variable that was most predictive of the Wexner score at 4 year. There are no systematic reviews or randomised

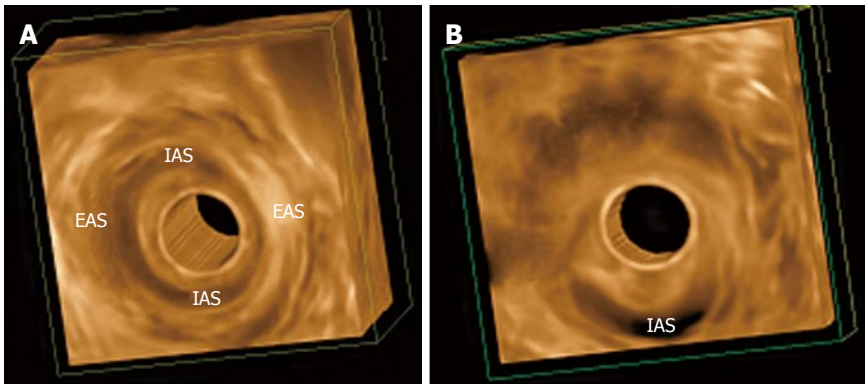

Figure 2 Three-dimensional endoanal ultrasonography images. A: Normal appearance of the external anal sphincter (EAS) and internal anal sphincter (IAS); B: An IAS defect in woman as a complication of a previous anorectal surgery (due to fistula).

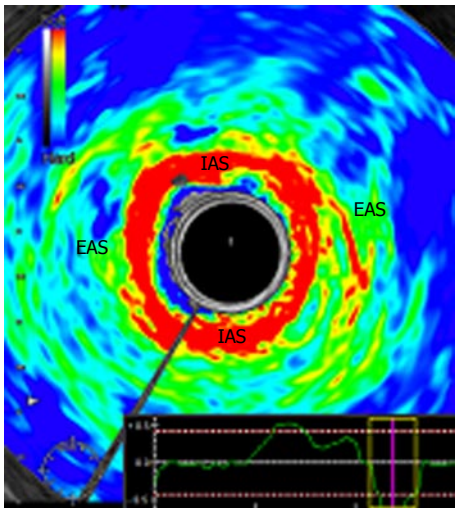

Figure 3 Normal appearance of the internal and external anal sphincters in endoanal ultrasound real-time elastography. The internal anal sphincter appears in red (softer) and external anal sphincter in green/blue (harder). EAS: External anal sphincter; IAS: Internal anal sphincter.

controlled trials to suggest the best method of follow-up after obstetric anal sphincter repair[22].

EAUS can also be important to aid decision for future delivery. According to the RCOG guidelines[22], "all women who have sustained an OASIS in a previous pregnancy and who are symptomatic or have abnormal EAUS and/or manometry should have the option of elective caesarean birth. Between 17% and 24% of these women with previous third-degree tear developed worsening fecal symptoms after a second vaginal delivery".

THREE-DIMENSIONAL EAUS

Three-dimensional EAUS has been used in the evaluation of the anal canal since the late 1990s[33,34]. Before 3D, imaging of the anal canal was mainly limited to the axial plane, impairing accurate longitudinal measurement, which is important for complete surgical repair. Three-dimensional EAUS produces a digital volume that can be seen from any plane, allowing length, thickness, area, and volume measurement (Figure 2).

Christensen *et al*[35] conducted a study to investigate the differences of 3D and 2D EAUS in visualizing damage to the anal sphincter complex. The agreement between the two observers that evaluated the images was better when using 3D (98.2% using 3D and 87.9% using 2D), so 3D improved diagnostic confidence.

The studies involving 3D EAUS also allowed for a better understanding of sex differences in sphincter configuration and between parous and non-parous females, continent and incontinent patients[36]. FI was not associated with loss of sphincter volume, but anterior sphincter length and EAS thickness is smaller[36]. Williams *et al*[37] assessed changes to anal canal morphology after delivery, in the absence of sphincter trauma, and there was a decrease in the length of the anterior portion of the EAS following childbirth.

ULTRASOUND REAL-TIME ELASTOGRAPHY

Real-time elastography (RTE) has been evaluated previously in tumours and inflammatory tissues, and has proven to provide valuable additional information.

In 2010, Allgayer *et al*[38] performed the first study to access RTE in FI, 50 patients were included. The IAS, a smooth muscle, consisted of softer areas (red) than the EAS and, conversely, the EAS, a striated type of muscle, contained harder elements (blue) than the IAS (Figure 3). There was an absence of a correlation of elastogram color distributions of the IAS and EAS with major clinical, functional and gray-scale B-mode parameters, so RTE did not seem to provide additional information in the diagnostic workup of FI. However, there was a non-significant increase in the percentage of blue (hard) areas in the IAS in patients neoadjuvantly irradiated for rectal or cervical cancer compared to non-irradiated patients. To confirm this data, the authors performed a larger study[39], but RTE with quantitation of sphincter elastic properties yielded no further diagnostic and prognostic information compared to

conventional EAUS in irradiated and non-irradiated patients and, therefore, cannot be regarded as a new tool in the assessment of those patients.

Hence, currently there is not evidence to support the use of RTE in FI evaluation.

CONCLUSION

FI is a serious clinical and social problem, frequently under-reported, and clinicians need to be more alert to it in the routine clinical practice. EAUS is a fundamental tool when assessing these patients.

The most important cause of FI is obstetric injury and the more relevant questions and controversies in EAUS are related to this aetiology. The diagnosed of sphincter injury after delivery and after complete primary repair is much lower to that found by EAUS, and many of these women developed FI, later in life.

While three-dimensional EAUS is currently accepted for sphincter evaluation in FI, there is presently no evidence to support the use of elastography.

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REVIEW

Cholangiocarcinoma and malignant bile duct obstruction: A review of last decades advances in therapeutic endoscopy

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Abstract

In the last decades many advances have been achieved in endoscopy, in the diagnosis and therapy of cholangiocarcinoma, however blood test, magnetic resonance imaging, computed tomography scan may fail to detect neoplastic disease at early stage, thus the diagnosis of cholangiocarcinoma is achieved usually at unresectable stage. In the last decades the role of endoscopy has moved from a diagnostic role to an invaluable therapeutic tool for patients affected by malignant bile duct obstruction. One of the major issues for cholangiocarcinoma is bile ducts occlusion, leading to jaundice, cholangitis and hepatic failure. Currently, endoscopy has a key role in the work up of cholangiocarcinoma, both in patients amenable to surgical intervention as well as in those unfit for surgery or not amenable to immediate surgical curative resection owing to locally advanced or advanced disease, with palliative intention. Endoscopy allows successful biliary drainage and stenting in more than 90% of patients with malignant bile duct obstruction, and allows rapid reduction of jaundice decreasing the risk of biliary sepsis. When biliary drainage and stenting cannot be achieved with endoscopy alone, endoscopic ultrasound-guided biliary drainage represents an effective alternative method affording successful biliary drainage in more than 80% of cases. The purpose of this review is to focus on the currently available endoscopic management options in patients with cholangiocarcinoma.

Key words: Cholangiocarcinoma; Malignant bile duct obstruction; Interventional endoscopy; Endoscopic therapy; Self-expandable metal stent

Core tip: Cholangiocarcinoma are an heterogeneous group of tumor and represent a challenge in medicine because of the difficulty in establishing the diagnosis and an high recurrence rate after surgery which represents the only curative treatment. Endoscopy has gained a

pivotal role in the management of the disease, before surgery if patient is amenable to surgical intervention or in those unfit for surgery. New stent prototype able to release drugs and/or photodynamic therapy have been commercialized with promising results. When endoscopy fails, endoscopic ultrasound-guided biliary drainage represents an effective alternative method affording biliary drainage.

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INTRODUCTION

Cholangiocarcinoma (CC) is an epithelial malignancy with markers of cholangiocyte differentiation arising within the biliary tree. It is characterized by a marked genetic heterogeneity which explains its high therapeutic resistance[1]. CC is rare but related mortality is high because it is most often diagnosed at a locally advanced stage, not amenable to curative surgery.

Although the incidence of CC is rapidly increasing it remains a rare disease. Data about endoscopic therapeutic options are often comprised into large databases of malignant obstructive jaundice mainly due to pancreatic head cancer. This may have influenced the reported outcomes and benefits of endoscopic treatment modalities[2].

Currently, classification of CC is based on anatomical site, defining intrahepatic, perihilar and distal CCs[2]. Intrahepatic CC is defined as a tumor located proximally to the branch of the right and left lobe bile ducts; the extrahepatic and perihilar cholangiocarcinoma is localized to the area between the second branches bile ducts and the insertion of the cystic duct into the common bile duct (Figure 1); whereas distal CC is confined to the area between the origin of the cystic duct and the ampulla of Vater[3].

Several progresses in the management (diagnosis, treatment and palliation) of CC have befallen in the last decades. However, surgical resection or liver transplantation represents the only potential curative alternative for all subtypes of CC[2]. Unfortunately, involvement of the vascular structures and lymphnodes is associated with very low 5-year survival rates even after curative-intent surgery[2] and, overall the clinical results of patients undergoing liver resection are disappointing with a survival rate of 20%-35% within 5-year[4-9]. Palliative therapy, in patients not amenable of surgical intervention includes systemic chemotherapy and loco regional therapies (TACE, RFA) to reduce masses but increased survival rate has not yet been shown[2].

Figure 1 Distal cholangiocarcinoma during endoscopic retrograde cholangiography.

The main onset of CC is unpainful icterus in > 90% of patients and preoperative biliary drain (endoscopic or percutaneous), has been introduced because jaundice is thought to increase the risk of postoperative complications, but the advantages of this procedure are still unclear[10]. Moreover, in patients who will undergo neo-adjuvant therapy the work-up preceding chemotherapy includes biliary stenting. In the last decades advances in stenting materials and acknowledgement of the benefits in the post-surgical outcome due to pre-operative biliary drainage has led endoscopic retrograde cholangiography (ERC) to a pivotal role in the work up of CC, both in patients amenable to surgical intervention and in those unfit for surgery.

EPIDEMIOLOGY

The reported incidence in the United States is one or two cases per 100000 person/year, also in Europe is 1.5 per 100000 person/year, and it accounts for approximately 3% of all gastrointestinal malignancies. CC is the most common primary malignancy of the liver after hepatocellular carcinoma. An increase in intrahepatic CC mortality has been registered worldwide particularly in western compared with central and northern Europe. The increased incidence of intrahepatic CCs may in part be attributed to new diagnostic methods for obstructive jaundice allowing to identify biliary malignancies which previously would have gone undetected. In spite of this, the rising incidence of intrahepatic CC has not been associated with an increased proportion of early stage or small size lesions[11-15].

Perihilar disease represents about 50%, distal disease 40% and intrahepatic disease less than 10% of CC cases. Age-adjusted rates of CC are reported to be the highest in Hispanic and Asian populations (2.8-3.3 per 100000 person/year) and lowest in non-Hispanic white people and black people (2.1 per 100000 person/year)[2].

RISK FACTORS

The main risk factors are considered primary sclerosing

cholangitis (PSC) and choledochal cysts. The per-year cumulative risk of CC in patients with PSC is 1.5% after the development of jaundice and the prevalence of CC in patients with PSC ranges between 8% and 40%. A recent study from the Netherlands showed that the risk of CC for patients with PSC is 9% after 10 years from the time of the diagnosis[13]. However for the majority of patients a specific risk factor has not been identified. Recently, cirrhosis and viral hepatitis have also been proposed as potential risk factor, particularly for intrahepatic CCs[2]. Another risk factor for the development of CC are choledochal cysts (incidence of CC is between 10% and 20%), significantly reduced by early diagnosis and surgical ablation[15]. The carcinogenetic pathway is not clear although biliary stasis and reflux of pancreatic fluids are suspected through chronic inflammation way[1]. Unfortunately, CC can also occur years after resection of the cyst suggesting some genetic abnormality predisposing to the development of biliary neoplasia[16].

MANAGEMENT

CC have an remarkably poor five-year survival rate estimated from 5% to 10%. Some difference could be detected if survival is stratified by location of the lesion: the percentage of patients amenable of surgical resection is higher if the location is distal CCs compared to proximal (intrahepatic and perihilar) tumors. Nakeeb *et al*[17] published a large series about resectability rates for distal, intrahepatic, and perihilar lesions: 91%, 60%, and 56%, respectively[17]. Moreover patients who undergo a potentially curative resection, at pathology examination achieve tumor-free margins barely in 20% to 40% of proximal and 50% of distal location[18]. These percentage are even lower if a proximal tumor-free margin of at least 5 mm is requested as a curative criteria.

Surgery data for CCs have increased over year, largely owing to more aggressive surgery strategies and extended criteria for resectability.

Criteria for resectability of CC in the United States include[19]: (1) absence of retro-pancreatic and celiac nodal metastases or distant liver metastases[20]; (2) absence of portal vein or main hepatic artery involvement; (3) absence of extrahepatic adjacent organ invasion; (4) absence of spread disease; however, resectability is finally determined at surgical exploration, particularly with perihilar tumors[21]. Due to their location within the upper hepatoduodenal ligament, these tumors often extend into the liver and major vascular structures, and preoperative evaluation of resectability is often difficult. Thus, surgical exploration is indicated for proximal bile duct carcinomas whenever feasible.

Whether preoperative biliary decompression using an endoscopically or percutaneously placed stent should be carried out in patients who present with obstructive jaundice is still controversial and will be discussed below. Obstructive jaundice is the most common presenting symptom of CC. If biliary drainage is advantageous or not is still under debate. Cholestatic malabsorption, liver dysfunction, and biliary cirrhosis develop rapidly with unresolved obstruction and severe liver dysfunction is one of the main factors that increase postoperative morbidity and mortality following surgical resection[21].

The European Society of Gastrointestinal Endoscopy (ESGE) focused his attention on the treatment options in order to select the most appropriate procedure (with or without sphincterotomy) and stent choice (plastic or metal, short or long) on the basis of patient's disease stage and tumor location.

ENDOSCOPIC TREATMENT IN PATIENTS ELIGIBLE FOR SURGERY

Preoperative biliary drainage was introduced to improve the postoperative outcome, for the reason that patients with jaundice had an increased risk of postoperative complications[10-22]. In various experimental studies and retrospective case series, preoperative biliary drainage reduced morbidity and mortality after surgery[23-25]. Nevertheless, two meta-analyses of randomized trials and a systematic review of descriptive series showed that the overall complication rate in patients undergoing preoperative biliary drainage was higher than in those who were referred straight to surgery[26]. In patients, fit for surgery for malignant common bile duct (CBD) obstruction, introduction of a plastic biliary stent followed by postponed surgery was associated with a higher morbidity compared with surgery within 1 wk. This was partly explained by complications associated with the biliary drainage procedure itself. Nevertheless, in many institution preoperative biliary drainage has been incorporated into the work-up of cancer of the pancreatic head or distal CBD[27]. In 2010 van der Gaag *et al*[10] conducted a large multicenter randomized trial in which 202 patients were randomized to receive whether preoperative biliary drainage followed by surgery within 4-6 wk, or surgery alone within 1 wk of diagnosis. Serious complications were registered in 39 percent in the immediate surgery group and 74 percent in the group with biliary drainage (RR = 0.54, $P < 0.001$)[28]. Neither mortality nor length of hospital stay were reduced in patients who underwent preoperative drainage. Moreover, the presence of a stent within the biliary tree could decrease the accuracy of diagnostic imaging to predict tumor resectability and the surgeon's ability to determine the proximal tumor extent during intervention.

The ESGE recommends preoperative biliary drainage only in patients who will undergo neo-adjuvant therapies or in patients with biliary sepsis, or in patients with troublesome itching or predicted delay in surgical intervention[29-50].

How to achieve biliary drainage: endoscopically or *via* a percutaneous approach? Retrospective series and at least two prospective trials conducted in patients with

obstructive jaundice from a malignant hilar obstruction (mainly proximal CCs or gallbladder cancer) suggest that successful palliation of jaundice is more likely and the incidence of post-procedure cholangitis may be lower with the percutaneous as compared to the endoscopic approach[31-33].

Endoscopic biliary drainage can be obtained using either plastic or self-expandable metal stents (SEMSs). Many stents (plastic and metal, both covered and uncovered), are available and both produce similar short-term results with respect to clinical success, morbidity, mortality, and improvement in quality of life[50]. A systematic review concluded that neither stent type offered a survival advantage[34]. Accordingly, in patient candidate for surgery the choice of stent should be guided by tumor location and extension.

The use of a plastic stent is inexpensive and effective, and the stent can be easily removed or replaced. Plastic stents, however, eventually develop occlusion by sludge and/or bacterial biofilm, and maintaining biliary drainage with plastic stents usually requires repeated endoscopic procedures. Plastic stents are available in multiple diameters ranging from 7 to 11.5 French, though 10 French stents are the most commonly used for distal common bile duct obstruction[35]. SEMSs provide a larger opening diameter than plastic one thus enabling prolonged patency and rapid biliary drainage[50]. However, the cost of metal stents is considerably higher and their removal may be challenging. The indications for using SEMSs in patients candidate to surgery is not well established yet. The main reason for the preferential use of plastic stents in patients with pancreatic cancer was the notion that uncovered SEMS could hinder pancreatoduodenectomy by interfering with transection of the bile duct proximal to the neoplasia[36]. With growing experience it has been shown that, when 2 cm or more of the common hepatic duct can be exposed proximally to the SEMS, the surgical procedure is not more complex than in the presence of a plastic stent[35].

Which kind of metal stent? SEMS models have been significantly developed and changed in the last decade: out of five types in use ten years ago, only single one is still available[29-37]. The distinguishing features of the various available SEMSs are prices, shortening ratio, radio-opacity, covering, radial force, flexibility, size of open cells of the mesh, anchoring mechanism and design of the tip[29-37]. *In vitro* measurements of radial expansion force and of flexibility have shown markedly different results between the various SEMSs, including covered and uncovered models of otherwise identical SEMSs[38]. The opening procedure shorten SEMSs by 0%-50%: different models with different shortening ratio are available. If the stricture is long and narrow the deployment could be difficult and irregular. Large open cells in the mesh may allow tissue to ingrow into the stent lumen, getting an inefficacious biliary drainage either immediately after the insertion or during follow-up[39-41]. Some special SEMS models, studied for hilar strictures, have a section with larger mesh cells in order to allow the introduction through the mesh of a new stent to reach another biliary branch[29]. In case of covered SEMSs, anti-migration mechanisms are particularly important: these may include flared ends or external fins, but some complications have been registered like bleeding of the bile duct wall caused by decubitus ulcers[42]. Recently models with soft ends and slip-knot to facilitate removal have been commercialized reducing the risk of bleeding or perforation if the wires are sharp and not fused.

ENDOSCOPIC TREATMENT IN PATIENTS WITH LOCALLY ADVANCED DISEASE

The long-term prognosis in CC patients who have undergone potentially curative surgical resection remains poor: these discouraging results have prompted interest in the use of neo-adjuvant therapy in patients amenable to surgery in order to improve survival. Such a strategy has also been proposed in locally advanced cases aiming to downstage the disease to allow surgical resection. This topic is valid for distal as well as for hilar CC. Recently in case of bilateral extension beyond the secondary radicles curative resection has been proposed after application of neoadjuvant therapy PDT oRFA (its applications and results will be discussed later).

The choice of the best stent to be used in this selected patient is less controversial than in those eligible for surgery. The efficacy of plastic stents is generally poor: more than one half of patients treated with plastic stents during neo-adjuvant therapy requires repeated stent replacement owing to stent occlusion or cholangitis[43]. Several studies have demonstrated that the use of SEMSs leads to improved outcome during neo-adjuvant therapy. Aadam *et al*[44] reported a 7 times higher complications rate and a 3 times higher hospitalization rate in patients treated with plastic stents as compared with patients treated with metal stents.

Uncovered and covered SEMSs are available. Uncovered SEMSs have a mesh design that allows them to be embedded in the biliary duct wall but it also makes them susceptible to tissue in-growth, which can lead to occlusion in as many as 20% of cases. Covered SEMSs were designed to prevent tissue in-growth but, as expected their use is associated with an increased rates of migration[45]. In an effort to guarantee patency and decrease rates of migration, partially covered SEMSs have been developed. In a recent meta-analysis, Saleem *et al*[46] concluded that covered SEMSs supply a significantly longer patency than uncovered SEMSs (average 60 d), but at the price of a higher migration rate[46-48]. Similar rates of cholecystitis were also found (approximately 2% in each group). Through subgroup analysis, Saleem *et al*[46] did not find any difference in rates of migration or stent patency comparing partially covered SEMSs to fully covered SEMSs. Contrastingly, in a retrospective cohort study analyzing the outcome

of 749 patients by Lee *et al*[47] no difference in stent obstruction was found (covered SEMSs 35%, uncovered SEMSs 38%) . While obstruction due to tumor in-growth was more frequent in patients treated with uncovered SEMSs (76% *vs* 9%, $P < 0.001$), other mechanisms of obstruction occurred in patients treated with covered SEMSs, including sludge formation and food debris. Conversely, higher rates of migration (36% *vs* 2%, $P < 0.001$) and of acute pancreatitis (6% *vs* 1%, $P < 0.001$) were found in patients treated with covered SEMSs[47]. This study was retrospective and open, and follow-up was not standardized. In a recent study, Kitano *et al*[48] used a covered SEMS modified to reduce migration. The anti-migration characteristics consisted of low axial forces and uncovered flare ends, and was compared to uncovered SEMSs of similar design. One hundred and twenty patients were included in this prospective randomized multicenter study and the covered SEMS group had a substantial longer stent patency (mean of 219.3 d *vs* 166.9 d, $P = 0.047$) and less need for re-intervention (23% *vs* 37%, $P = 0.08$) compared to uncovered SEMSs. The tumor ingrowth was also lower in the covered SEMS group (0% *vs* 25%, $P < 0.01$)[47,48].

Even if a lower complication rate and a lower hospitalization staying has been described in patients with SEMS compared with plastic stents, the management of long standing metallic stent is challenging due to ingrowth of neoplastic tissue. Usually patients with positioned SEMS underwent neoadjuvant therapy to achieve a tumor downstaging and even if a 5-year survival rate is not influenced a prolonged survival is described and stent obstruction occurs frequently. Management of stent obstruction is challenging especially in hilar CC when previous bilateral SEMS have been positioned, due to the difficulties in bypassing the stent with the guidewire without enter the stent mesh. If not possible an option could be the ballon dilation of stent mesh.

ENDOSCOPIC TREATMENT IN PATIENTS WITH ADVANCED DISEASE

Placement of a stent is currently considered the treatment of choice for palliation of malignant obstructive jaundice in patients with advanced CC since it is associated with similar rates of jaundice relief and survival but less morbidity compared to the surgical approach[49-59]. Successful endoscopic deployment of a stent (or multiple stents as needed to span the malignant stricture) is possible in 70% to 100% of patients. Pre-procedure CT and/or MRI is often used in an attempt to identify the dominant biliary system in the event that only one side can be drained endoscopically.

Endoscopic stenting has been compared to the percutaneous approach. Retrospective series and trials conducted in patients with obstructive jaundice from a malignant hilar obstruction (mainly proximal CCs or gallbladder cancer) suggest that successful palliation of jaundice is more likely and rates of early cholangitis may be lower with the percutaneous as compared to the endoscopic approach[60,61]. However, other complications may be more frequent (*e.g.*, bile leaks and bleeding), potentially increasing morbidity and mortality. Furthermore, percutaneous stents usually imply an open external drainage, at least initially, and this is often inconvenient to the patient. As a result, in most institutions an initial endoscopic attempt at drainage is usually preferred whenever possible.

Figure 2 Endoscopic retrograde cholangiography with a plastic stent in the right hepatic duct. However the left hepatic duct remains dilated.

Palliative endoscopic biliary decompression can be achieved using either plastic or SEMSs. In the last two decades, SEMSs have been increasingly used and have been demonstrated to be more effective than plastic stents allowing a more rapid biliary drainage and consequently a lower incidence of septic complications since the first procedure[51,52]. A systematic review concluded that none stent improves survival rate however uncovered metal stents have a lower risk of causing cholecystitis and pancreatitis and migration rate is significantly lower than in covered group[31].

Whether to use unilateral or bilateral stents in patients with hilar obstruction is debated. The issue should be to drain as much as possible but this does always mean that you need to put a stent in every single duct. In many cases, unilateral stent placement will be sufficient to relieve jaundice and frequently, a dominant duct could be identified during ERC procedure, as the more effective to be drained (Figure 2)[32]. However, unilateral drainage alone may not relieve jaundice completely and may increase the risk of cholangitis especially if contrast medium have been injected and not drained. Studies comparing these approaches have reached variable and dubious conclusions. Many endoscopists place bilateral stents (plastic or metal); certainly a minimum of two stents (left and right branches) is need in an attempt to maximize biliary drainage (Figure 3). The choice to use more than two stents is linked to patient disease features and endoscopist skill.

RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) has been used to treat

Figure 3 Use of covered self-expandable metal stent in patients with hylar cholangiocarcinoma.

liver malignancies since the early 1990s[61-65]. More recently this technique has been applied in malignant biliary strictures[62].

Habib TM Endo-HPB EMcision is an endoscopic bipolar catheter studied to be introduced through biliary malignant strictures, so that radiofrequency energy can be delivered locally before stent positioning. Potential advantages of the device use could be longer stent patency by ease down tumor growth. Endo-HPB is a 8 F, 1.8 m coaxial over the wire catheter that is designed to be inserted through a 3.2 mm working channel of the endoscope. At the distal end of the catheter, two ring electrodes spaced 8 mm apart produces a heating zone length of approximately 25 mm.

RFA in bile duct appears to be safe however its efficacy in long term and its role, alone or combined with SEMS is unclear. Sharaiha *et al*[64] recently compared RFA combined with SEMS with SEMS alone in 66 patients. Twenty-six were treated with RFA and SEMS and 40 only with stent placement. The author confirms a statistically significant improvement in malignant strictures diameter after RFA treatment[63-65]. Randomized controlled trials are needed.

ALTERNATIVE STENT DESIGN AND STRATEGIES

Recently Shah[65], proposed drug-eluting stents designed to improve SEMS patency by delivering a chemotherapeutic agent such as paclitaxel to prevent tumor in-growth and stent occlusion[66]. Unfortunately, in a multicenter prospective study comparing drug-eluting covered SEMSs with covered SEMSs no significant difference in stent patency was found[67].

PHOTODYNAMIC THERAPY AND DRUG ELUTING STENT

Photodynamic therapy (PDT) is a new palliative technique for malignant bile duct stenosis that seems to improve pain relief, increase biliary patency and increase survival.

Recently Bae *et al*[2] proposed a photosensitizer-embedded self-expanding metal stent (PDT-stent) which provides a photodynamic treatment without the need of systemic injection of photosensitizer and the treatment could be repeated more than one time due to the incorporation of the polymeric photosensitizer into the mesh of the stent. Photo-fluorescence imaging of the PDT-stent demonstrated homogeneous distribution of polymeric Pheo-A (PPA) on stent surface and the stent maintained its photodynamic power at least for 8 wk, for repeated PDT procedure if necessary after stent positioning. The PDT-stent after light exposure created cytotoxic free radical such as singlet oxygen in the close tissues, inducing destruction of neoplastic cells on animal models[66,67].

EUS GUIDED BILIARY DRAINAGE

Endoscopic biliary drainage with stent positioning is technically successful in > 90% of procedure. In the case of failure, endoscopic ultrasound (EUS)-guided biliary drainage has recently emerged as an effective alternative method providing technical success in > 80% of cases[49]. EUS-guided biliary drainage was first reported in 2001 by Giovannini *et al*[67] and can be approached into 3 different ways: (1) EUS-guided transluminal biliary drainage including choledoco-duodenostomy and hepatico-gastrostomy; (2) EUS-rendezvous technique; and (3) EUS-antegrade approach[67,68].

For EUS-guided transluminal biliary drainage, the biliary duct is punctured from the proximal duodenum with a 19 G fine needle aspiration (FNA) under EUS guidance followed by cholangiography. Progressively a guidewire is driven into the biliary system and dilation of the needle way is carried out. After fistula creation with a cystotome, or a bougie dilator, the stent is deployed between the biliary duct and the duodenal lumen for biliary drainage.

In EUS-rendezvous technique, the biliary duct is approached under EUS and X-ray guidance *via* 19 G FNA needle. Progressively, a guidewire is driven into the biliary system then through the bile duct, through the ampulla within the duodenum. After guidewire positioning, ERCP is performed using guidewire and the guidewire is retrieved, once biliary cannulation is carried out or the stenosis has been exceeded. Therefore, EUS- rendezvous technique is feasible only in patients in which the endoscopic access to the ampulla is preserved[68].

In EUS-anterograde approach, the intra-hepatic biliary duct is accessed from the small bowel with creation of a temporary fistula between the small bowel and the intra-hepatic biliary duct then the stent placement is achieved through the fistula. This technique is appropriate for patients with surgically altered anatomy or duodenal obstruction which prevent ampullary access.

Published studies regarding choledoco-duodenostomy

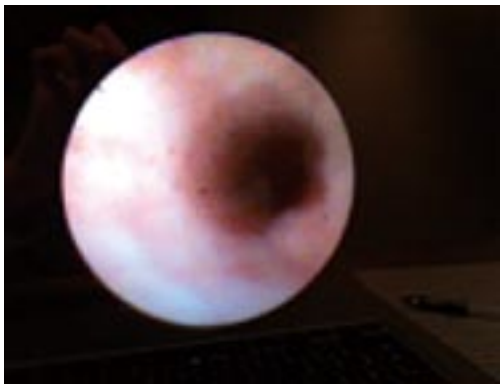

Figure 4 Visualization of biliary epithelium during SpyGlass.

and hepatico-gastrostomy show technical success rates of 94% and 87% with early complication rates of 19% and 27%, respectively, despite the fact that different biliary access and fistula dilation methods have been utilized. Regarding stent type, covered SEMS have generally been preferred over plastic stents, especially in more recent studies. Radial expansion of covered SEMSs can reduce risk of complications such as bile peritoneal leak or pneumoperitoneum because the fistula is immediately plugged by the covered SEMS. On the other hand, stent migration is reported after endoscopic procedure. For this purpose, the development of stents specifically designed for these procedures could further improve the results.

One of the most challenging aspects of EUS-rendezvous technique is the guidewire manipulation, which requires skill, tact sensitivity and good cooperation with a second operator[66]. Similarly, EUS-antegrade approach requires careful guidewire manipulation, however a major care is the risk of bile leak into the peritoneal cavity through the dilated fistula even if no report of biliary peritonitis have been issued, and the overall success and complication rates are 77% and 5 %, respectively[69-73].

NEW TECHNIQUES

Cholangioscopy

Peroral cholangioscopy, "mother-baby" technique, was utilized in the mid-1970s for the diagnosis and definition of bile duct narrowing. Nevertheless this technique revealed many limitations in visualization of the wall and required the cooperation of two skilled operators[74,75]. The "SpyGlass system" (Boston Scientific Corp, Natick, MA, United States) introduced in 2006 has enlarged the role of cholangioscopy from a diagnostic to a therapeutic one. The new system has overcome the need of two endoscopists and it has been launched as a single endoscopist cholangioscope. It allows the direct visualization of biliary tree (Figure 4) and consequently its use in the diagnostic work up of CC is well established. Sethi *et al*[74] reported a diagnostic accuracy of SpyGlass around 57% and these data were confirmed also in other series with an overall diagnostic accuracy, in differentiating neoplastic *vs* non neoplastic lesions, varied from 77% to 90%[75-79]. Although it is considered limitative to banish a cholangioscope to a diagnostic role in CC work up, more data are needed about its role in therapeutic endoscopy and biliary drainage. One of the main indications is the lithotripsy for difficult to remove, biliary stones[80]. Recently Dong Choon Kim described the use of an ultraslim endoscope (GIF-XP260N; Olympus, Tokyo, Japan) for intraductal stones fragmentation under endoscopic visualization[81].

Fluorescence in situ hybridization

Fluorescence *in situ* hybridization (FISH) assesses the presence of chromosomal aberrations, in number or structures, and uses fluorescence-labeled probes to evaluate increases or decreases in chromosome number if referred to numerical abnormalities or to specific structural abnormalities in case of clonal diversity[82,83]. This technique is performed on ERC brushing smears.

Previous studies have demonstrated that FISH polysomy combined with cytology improves sensitivity. Some studies have considered the positive FISH results based on polysomy only, whereas some have considered trisomy or tetrasomy as a positive test results as well. Recently a review was published by Navaneethan *et al*[82] with a pooled sensitivity and specificity was 51% and 93% in detection of CC in patients with PSC. Vasilieva *et al*[83] in 2013 published data about the use of structural abnormalities as markers of clonal diversity and different clinical features of the disease. However more data are needed, the use of fish does not increase sensitivity significantly. A future role of the FISH will be the possibility to delineate the oncogenesis, to understand the response or not to chemotherapy[83,84].

CONCLUSION

Cholangiocarcinoma and bile duct tumors are an heterogeneous group of tumor with different biological behavior and prognosis according to their location and growth pattern. CC presents a special challenge in gastroenterology, oncology, and visceral surgery because of the difficulty in establishing the diagnosis, local complications in the biliary pathways, and a high recurrence rate after resection. Diagnosis is usually defined in advanced disease stage, due to paucisintomaticity of tumor and to low sensitivity of imaging technique for detection of lesions at early stage. The only curative treatment for CC is surgery, but 40%-85% of all patients have recurrent disease even after radical excision. Because of this high recurrence rate and because the majority of patients undergo palliative therapy (chemotherapy or endoscopic therapy) to try to downstage the tumor and adjuvant treatments are now under intense discussion. Moreover because of the low prevalence of the disease, there have been only a few studies of palliative chemotherapy for CC. On the basis of one positive phase 3 study, chemotherapy with

gemcitabine and cisplatin is considered the standard and now plays an established role in palliative care[84].

Endoscopy, as explained in this review has gained in the last decades a key role in the work up of CC, both in patients amenable to surgical intervention as well as in those unfit for surgery or not amenable to immediate surgical curative resection owing to locally advanced disease. Endoscopy allows successful biliary drainage and stenting in more than 90% of cases. The development of new stents, metallic, covered, with different mesh materials, different mesh shape is a constant work in progress to reduce complications in patients with advanced disease, to avoid repeated endoscopic procedure and to improve long term results. Moreover in the last two years new stent prototype able to release drugs and/or photodynamic therapy have been commercialized with promising results but very few data are available, not enough to be validated. When endoscopy fails, endoscopic ultrasound-guided biliary drainage represents an effective alternative method affording successful biliary drainage in more than 80% of cases. Also in this field new dedicated stents fit for trans-duodenal biliary drainage or trans-hepatic biliary drainage are under construction.

This a new field that need constant updating and future studies should address the efficacy of combined local and systemic treatments.

In conclusion the final messages are: (1) The benefit of adjuvant chemotherapy has not yet been confirmed and require further investigation; and (2) Endoscopic biliary drainage by means of ERC is an integral component of the treatment of CC.

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REVIEW

Management of primary achalasia: The role of endoscopy

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Abstract

Achalasia is an oesophageal motor disorder which leads to the functional obstruction of the lower oesophageal sphincter (LES) and is currently incurable. The main objective of all existing therapies is to achieve a reduction in the obstruction of the distal oesophagus in order to improve oesophageal transit, relieve the symptomatology, and prevent long-term complications. The most common treatments used are pneumatic dilation (PD) and laparoscopic Heller myotomy, which involves partial fundoplication with comparable short-term success rates. The most economic non-surgical therapy is PD, with botulinum toxin injections reserved for patients with a higher surgical risk for whom the former treatment option is unsuitable. A new technology is peroral endoscopic myotomy, postulated as a possible non-invasive alternative to surgical myotomy. Other endoluminal treatments subject to research more recently include injecting ethanolamine into the LES and using a temporary self-expanding metallic stent. At present, there is not enough evidence permitting a routine recommendation of any of these three novel methods. Patients must undergo follow-up after treatment to guarantee that their symptoms are under control and to prevent complications. Most experts are in favour of some form of endoscopic follow-up, however no established guidelines exist in this respect. The prognosis for patients with achalasia is good, although a recurrence after treatment using any method requires new treatment.

Key words: Achalasia; Endoscopic treatment; Dilation; Botulinum toxin; Myotomy

Core tip: We propose a treatment and monitoring algorithm for achalasia based on the most relevant published evidence and an exhaustive summary of all the available endoscopic techniques.

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INTRODUCTION

Achalasia is a primary oesophageal motor disorder of unknown aetiology characterised manometrically by insufficient relaxation of the lower oesophageal sphincter (LES) and a loss of oesophageal peristalsis[1] secondary to the degeneration of the myenteric plexus[2]. It should be suspected in patients who present with dysphagia, regurgitation of undigested food debris, respiratory symptoms, chest pain, and weight loss[3]. It is described at any age, but occurs most frequently between the ages of 20 and 40. There does not appear to be any association with sex or ethnicity. The annual incidence is 1 in 100000 persons and the prevalence is 10 in 10000[4,5]. Following clinical suspicion and diagnostic confirmation by means of a barium swallow and manometry, the indication of oesophagogastroduodenoscopy (EGD) in the initial phase is essential for differential diagnosis, ruling out pseudoachalasia due to malignant neoplasms and the presence of oesophageal squamous cell carcinoma as complications of achalasia. Diagnosis using high-resolution manometry and multi-channel intraluminal impedancemetry appears to have a higher diagnostic sensitivity than conventional manometry in diagnosing this disease. It also allows the identification of subtypes: Type I is associated with absent peristalsis and no discernible esophageal contractility in the context of an elevated integrated relaxation pressure (IRP). Type II is associated with abnormal esophagogastric junction (EGJ) relaxation and panesophageal pressurisation in excess of 30 mmHg. Type III achalasia is associated with premature (spastic) contractions and impaired EGJ relaxation[6].

EGD forms an essential part of the diagnostic algorithm of achalasia, although in the earliest stage it has a low sensitivity for detecting this condition as up to 40% of patients with achalasia will have a normal endoscopy[7]. The presence of oesophageal dilation on the oesophagogram, a narrowing of the oesophageal junction into a "bird beak" shape, aperistalsis, and difficulty in evacuating the barium column from the oesophagus support the diagnosis[4]. The objective of treatment is to relieve the symptoms, improve oesophageal evacuation, and prevent the development of complications. Therapeutic options include medical treatment, endoscopic treatment, including pneumatic dilation (PD) and botulinum toxin injection (BTI), and surgical LHM treatment[5]. Other treatments with a promising future which are currently being researched are POEM, oesophageal stents, and ethanolamine injection.

ENDOSCOPIC THERAPY FOR ACHALASIA

Pharmacological endoscopic therapy

BTI (Botox, Allergan, Inc.) has been the most frequently used pharmacological endoscopic treatment for achalasia since 1995. Botulinum toxin is a neurotoxin which blocks the release of acetylcholine from nerve endings by cleaving the SNAP-25 protein. This causes a chemical denervation of the LES muscle, which can last several months, reducing its basal pressure[8,9]. The technique involves injecting 80 to 100 U of toxin in four quadrants (20-25 U in each) using a sclerotherapy needle, at a distance of 1 cm above the squamocolumnar junction. Higher doses have not been shown to be more efficient[10]. The initial response rate is very high, approximately 80%-90% in the month of treatment, but the therapeutic effect disappears over time such that < 50% of patients are asymptomatic after one year of monitoring[10-12]. This suggests that repeated treatments with the toxin are required every 6-12 mo. The predictive factors of a better response to treatment with BTI are: age > 40 years, achalasia type II, and a decrease in base line pressure of the LES after treatment[12]. BTI has not been shown to halt progressive oesophageal dilation, so it does not prevent long-term complications of achalasia. It is a simple, safe and effective technique with few side effects, although chest pain following injection has been described in 16%-25% of cases. Complications such as mediastinitis or allergic reactions to egg protein are rare, and systematic neurotoxicity with generalised paralysis does not occur due to the low doses used. However, repeated botulinum toxin treatments cause an intramural inflammatory reaction at the level of the LES as well as submucosal fibrosis which may make it more difficult to carry out subsequent surgical myotomy[13-15]. Treatment with BTI should therefore be reserved exclusively for patients of advanced age, those with high surgical risk, severe comorbidities, short life expectancy, and those who are not candidates for PD or surgical myotomy or on a waiting list for surgery[16].

PD

PD is the most effective non-surgical procedure in the treatment of achalasia[4,17]. The aim of dilation treatment is to rupture the muscle fibres of the LES by means of the force exerted by air balloons positioned and inflated at this level. Both the use of bougies as well as standard

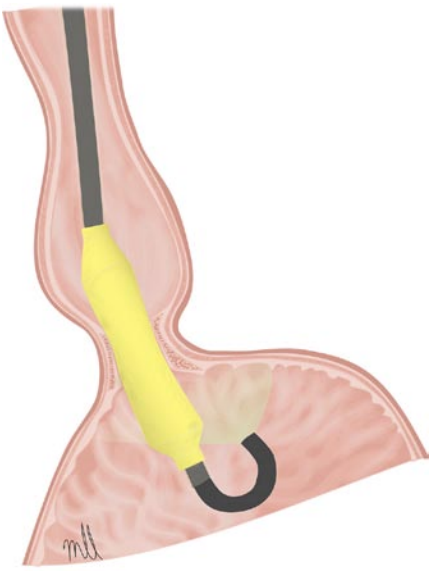

Figure 1 Witzel dilator.

balloon dilation through the endoscope channel (TTS balloon) have not been shown to be particularly effective in achieving this goal, which is necessary to significantly relieve symptoms[4]. The most commonly used dilation treatment for this disease is Rigiflex balloon dilation. Another type of balloon dilation used less frequently is the Witzel dilator, which has also been shown to be effective although it is less widely used and fewer papers have been published on it[18,19].

Pneumatic dilation with a Witzel balloon: Pneumatic dilation with a Witzel balloon is a relatively safe method of treating achalasia with a similar rate of complication to Rigiflex dilation, and a high level of efficacy in the medium to long term[18-20]. The Witzel dilator is a 15-cm polyurethane balloon with a maximum diameter of 4 cm, which is inserted attached to the endoscope until it is positioned at the level of the cardia using direct vision and retroflexion (Figure 1). According to the technique recommended by Alonso Aguirre[20] the balloon is inflated to 200 mmHg for 1 min and, depending on patient tolerance (if the dilation is performed under conscious sedation), it is inflated again once or twice to a maximum pressure of 200 or 300 mmHg. If the dilation is performed under deep sedation, the balloon is inflated to 200 mmHg for 2 min. In a study published for our centre in 2009[18], we observed a success rate of 85% after the first and second dilations (only required in 23% of cases). During the first 5 years of follow-up, 80% maintained the response, and the proportion decreased to around 60% after 10 years. The only variable related to a positive response in the long term was age (> 40 years). A small number of complications were reported: perforation in 4.2%, all treated conservatively, and the appearance of gastro-oesophageal reflux (GER) in the 10% who responded to treatment with proton pump inhibitors (PPI).

Dilation with Rigiflex balloon: The procedure has been standardised with the use of the Microinvasive Rigiflex balloon system (Boston Scientific Corp, Massachusetts, United States). These polyethylene balloons are available in 3 diameters (30, 35, and 40 mm), mounted on a flexible catheter which is positioned in the oesophagus using a guide placed with the help of an endoscope. Balloon inflation at the level of the LES can be controlled using radiology, radiopaque marking, or endoscopy (Figure 2).

The protocol for inflating the balloon varies in function from centre to centre. In general, the balloon is inflated gradually until it reaches a pressure of approximately 7-15 psi, which is maintained for 15-60 s. Using radiology, it is possible to check how the central notch on the balloon, which corresponds to the LES, disappears as the balloon is progressively inflated[21]. This is the most important factor in order for the expansion to be effective, rather than the duration of balloon inflation[22]. Following PD, some authors recommend ruling out perforation by carrying out a radiological check using Gastrografin followed by a barium oesophagogram[4,23]. This technique can usually be performed on an outpatient basis. The patient may be discharged after 6 h, once complications have been ruled out[4,21]. According to some authors, it is possible to choose whether to perform a single dilation session[24], or to carry out successive dilations, progressively increasing the diameter of the balloon in each session (beginning with 30, then 35, and finishing with 40 mm)[25], with 4-6 wk between sessions, based on alleviation of symptoms, reduction of manometric pressure in the LES[24,26], or the improvement of oesophageal evacuation[27,28]. Overall, the results of the studies published show that PD is effective, with response figures of 40%-78% at 5 years and between 12%-58% at 15 years[29-31]. By using the strategy recommended in the clinical practice guidelines[4], higher response rates of up to 97% at 5 years and 93% at 10 years can be achieved[32]. The predictive factors for a failure of treatment with PD are: young patients (age < 40 years)[18,33,34], male sex, dilation using a 30-mm balloon, presence of pulmonary symptoms, failure of treatment after one or two dilation sessions[24,29,35,36], post-treatment determination of a pressure measurement in the LES > 10-15 mmHg, failure of the balloon to relax completely[37], or delayed oesophageal evacuation in a barium oesophagogram carried out in vertical position[26,38-41]. PD is the most cost-effective treatment for achalasia for a period of 5 to 10 years after the procedures[42,43]. Candidates for PD should be those for whom surgery is not contraindicated as a definitive treatment, given that the most severe complication for this technique is oesophageal perforation, which occurs in approximately 1.9% (range 0%-16%)[28,39]. Many perforations tend to occur after the first dilation and are believed to be related to incorrect positioning and balloon relaxation during dilation[44]. Early diagnosis

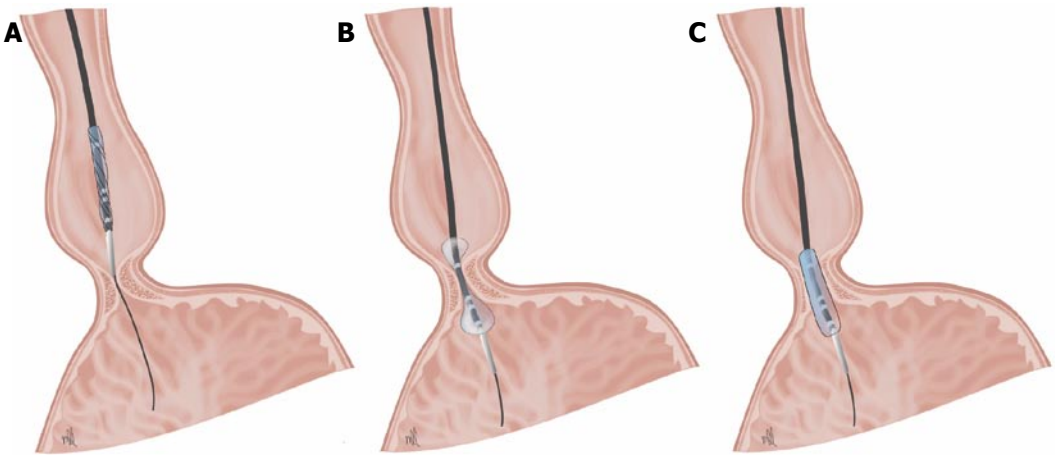

Figure 2 Dilation with Rigiflex balloon positioned at the level of the lower oesophageal sphincter. A: Step 1: positioning the balloon in the esophagogastric junction (EGJ); B: Step 2: deflated balloon in the EGJ; C: Step 3: inflated balloon in the EGJ.

of this complication favours an improved course. Small perforations can be managed conservatively with parenteral nutrition and antibiotics[45], however perforations which are larger, symptomatic, or with suspected contamination of the mediastinum must be repaired surgically *via* thoracotomy[4,21]. Other complications include GER, which is generally mild and transient, appears in 15%-35% of patients, and usually responds to treatment with PPI[46]. Serious GER complications following dilation are rare. Mild but frequent complications include chest pain, aspiration pneumonia, bleeding, fever, tearing of the oesophageal mucosa without perforation, and oesophageal haematoma.

Comparison of the different therapeutic modalities

Botulinum toxin *vs* pneumatic dilation: The results of individual randomised controlled trials comparing BTI and PD have shown that there are no significant differences between the two techniques in terms of remission of symptoms in the short term (4-6 wk), but there is a rapid relapse 6-12 mo after BTI. The success rate in the year of treatment varies from 65.8%-70% for PD and 24%-36% for BTI. However, it can be concluded that PD is more effective in the long term than BTI[11,47-50].

Botulinum toxin *vs* laparoscopic Heller myotomy: There are few studies comparing BTI with LHM. The study by Zaninotto *et al*[51] reports comparable efficacy at 6 mo, although at 2 years only 34% of patients treated with BTI remain asymptomatic, as compared with 87.5% of patients treated with LHM[51].

Role of combination therapy: Therapy with BTI in combination with any other type of endoscopic or surgical treatment for achalasia can increase the response rate. Although it is still not routinely recommended in clinical practice[52], Mikaeli *et al*[53] published a higher remission rate during follow-up in patients who had first been treated with toxin and then with PD (77%) compared to those who had only received treatment with PD (62%)[53]. Other authors have reported a higher percentage of remission after 2 years in those who had received PD first followed by BTI (56%) compared to those who had only received dilation (35.7%), or only toxin (13.79%)[54].

Pneumatic dilation *vs* laparoscopic Heller myotomy: The question of whether to choose surgical treatment or PD as the primary treatment option when treating achalasia remains controversial today. Numerous studies use the strategy of repeating dilation sessions depending on the symptomatic response, if there is no improvement in the manometric tests or in the evacuation of barium contrast. This strategy enables the response rates to be increased to levels comparable with those obtained with LHM[32,55,56]. The only randomised comparative study between PD and surgery, carried out by the European Achalasia Trial Investigators Group in 2011[57] showed similar results for both techniques with a follow-up period of 2 years. 201 patients were randomised to receive dilation with Rigiflex (n = 95) or LHM with partial fundoplication (n = 106). The success rate was comparable for both techniques after 1 year and after 2 years: 90% and 86% respectively for PD, and 93% and 90% for LHM (P = 0.46). The meta-analysis published in 2009 by Campos *et al*[49] includes non-randomised studies of case series. They reported overall response figures of 68% in the 1065 patients dilated with Rigiflex and 89% in the 3086 patients who underwent surgery. In a study by the Cleveland Clinic (Cleveland, OH, United States)[28], 106 patients were treated with PD and 73 patients with LHM. The success rate, based on clinical data or necessity of re-treatment, was similar for both groups: 96% for dilation *vs* 98% for surgery after 6 mo, decreasing to 44% *vs* 57% after 6 years. The advantages of endoscopic treatment are that it includes the possibility of outpatient care, is less invasive than surgery, involves fewer complications and less risk of subsequent reflux and haemorrhage. However,

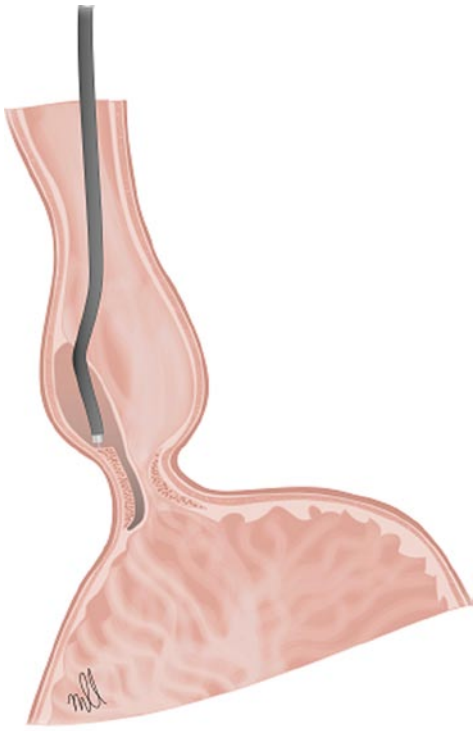

Figure 3 Peroral endoscopic myotomy.

in addition to the fact that more than one treatment session is frequently required, there are still no studies with long-term follow-up which have demonstrated the superiority of PD[21,58]. A recent meta-analysis published by Weber *et al*[59] found that both techniques, PD and LHM, were effective in the treatment of achalasia, however myotomy was found to be more durable[59]. There is some controversy around whether the initial PD obstructs the subsequent performance of laparoscopic myotomy[58,60]. The type of treatment must be selected consensually, taking into account the preferences of the patient as well as the experience of each centre[1,61]. These techniques should preferably be carried out by centres with a high volume and experience in LHM[58].

New treatments for achalasia

Peroral endoscopic myotomy: POEM is a minimally invasive procedure carried out *via* endoscopy. It combines the surgical principles of laparoscopic myotomy with the latest advances in endoscopic submucosal dissection[62].

The technique is performed under a general anaesthetic with endotracheal intubation and the patient in supine position. A liquid diet is indicated for 24-48 h prior to the procedure and antibiotic prophylaxis is administered on the day of the intervention, which is maintained during hospitalisation and in some cases for up to 7 d. Different authors agree on the use of CO_2 insufflation to minimise the risk of pneumomediastinum and air embolism. A submucosal injection of 10 mL of saline solution with 0.3% indigo carmine is administered in the central oesophagus, about 13 cm away from to the EGJ, in a 2 o'clock position. A longitudinal incision of 2 cm is made above the surface of the mucosa to gain access to the submucosal space (Figure 3). Thus a descending anterior submucosal tunnel through the EGJ is created, which reaches approximately 3 cm into the proximal stomach. Once the submucosal tunnel is complete, the circular muscle fibres are cut 2-3 cm in distal direction from the access to the mucosa, approximately 7 cm above the EGJ. Myotomy continues distally until it reaches the gastric submucosa, and extends about 2-3 cm in distal direction to the EGJ. Once the circular muscle fibres in the lower part of the oesophagus have been identified and cut, the site of access to the mucosa is closed using haemostatic clips[63].

The first reference to endoscopic myotomy for achalasia appears in 1980 in a case series published by Ortega *et al*[64]. Later, as endoscopic surgery through natural orifices (NOTES) progressed, Pasricha *et al*[12] demonstrated its feasibility using a porcine model. The technique was adopted in clinical practice in 2010 by Inoue *et al*[65]. The study evaluated 17 patients, aiming for a significant reduction in the index of symptoms of dysphagia in all of them (average score from 10 to 1.3; $P = 0.0003$), as well as the basal pressure of the LES (from 52.4 to 19.9 mmHg; $P = 0.0001$). The operating time ranged from 100 to 180 min, with an average myotomy length of 8.1 cm. No serious complications related to the procedure were described. One patient presented with a complication of pneumoperitoneum. After a follow-up of 5 mo, only one patient reported symptoms of reflux, which were shown in gastroscopy to be an oesophagitis Los Angeles Grade B, which was treated satisfactorily by taking a protein pump inhibitor[65,66]. In 2011, Swanström *et al*[67] published their experience with POEM in 5 patients. No leaks were detected in a barium oesophagogram 24 h after the procedure, nor were any complications described immediately post-operation, with all patients presenting a rapid relief of dysphagia without reflux symptoms[66,67]. In 2012, von Renteln *et al*[68] presented the results of the first prospective POEM trial in Europe. The myotomy was performed in 16 patients achieving a clinical response of 94% after 3 mo. The LES pressure was reduced from 27.2 to 11.8 mmHg ($P < 0.001$), with no patients developing reflux symptoms after the treatment[63,68]. Some authors have studied the applicability of the techniques to patients previously subjected to endoscopic treatment (BTI, PD). Sharata *et al*[69] demonstrated clinical success in this context in 12 patients. Only one case of intramural bleeding, which required a new endoscopy for haemostasis, and one case of dehiscence of the mucosectomy, which was treated with haemostatic clips, were described. All patients demonstrated symptomatic relief, with an average decrease in the Eckardt score from 5 to 1. Comparing these results with those of the 28 patients without previous endoscopic treatment, no significant differences were found to exist between the two groups[66,69]. In 2012, Zhou *et al*[70] published their experience with 12 patients with a history of

LHM in which they successfully performed endoscopic myotomy. No serious complications with the technique were described, achieving an average improvement in the index of symptoms from 9.2 to 1.3 ($P < 0.001$). The basal pressure of the LES was reduced from 29.4 to 13.5 mmHg ($P < 0.001$). Only one patient reported reflux symptoms, presenting a positive response to intermittent treatment with PPI[66,70].

The first study to retrospectively compare POEM and surgical myotomy was published in 2013. No significant differences were observed in terms of the length of the myotomy, complication rate, or hospital stay[63,71]. Bhayani *et al*[72] have recently presented the results of a study in which 101 patients were prospectively included, 64 treated with Heller myotomy and 37 with POEM. The authors conclude that the two techniques are comparable in terms of efficacy and safety, with similar results in post-operative manometry and pathological acid exposure, as assessed on an outpatient basis using a pH meter[72].

In summary, POEM is posited as a useful technique, although it is an expensive procedure which requires significant expertise. The studies published show excellent results in the short term as far as dysphagia relief and improvement of the manometric pressure data for the LES are concerned. The complication most frequently described is pneumoperitoneum, which can generally be resolved by conservative means. The presence of GER following POEM ranges between 5.9% and 46%, depending on the series, but in general it is a question of mild symptoms which can be adequately controlled with medical treatment. On the basis of the published data, it is no surprise that the majority of experts on POEM, including surgeons with extensive experience in surgical myotomy, appreciate the advantages of achieving results like those for LHM by minimally invasive means. Endoscopic myotomy could eventually become a first-line treatment for achalasia, except for those with significant comorbidity or advanced achalasia at the megaoesophagus stage. This technique is not a future anymore, but a present. However, new randomised studies are needed which will allow us to evaluate POEM in the long term and to compare the technique with the remaining treatment modalities.

Oesophageal prostheses: Self-expanding metallic prostheses have been used safely and effectively to treat malignant pathologies of the oesophagus and tracheoesophageal fistula, oesophageal perforations, and anastomotic leaks. However, given the high risk of complications (migration, perforation, indentation, and restenosis), its use in benign pathology is more controversial. Various authors have defended the use of removable prostheses in the management of benign stenosis of the oesophagus, arguing that it constitutes a reasonable alternative in the treatment of patients with achalasia[73,74]. The ideal prosthesis would be placed at cardia level to keep open the EGJ, thus limiting gastroesophageal reflux[75].

In 2009, Zhao *et al*[76] published their experience in 75 with a diagnosis of achalasia who were treated with the temporary placement of a self-expanding metallic prosthesis of 30 mm in diameter, with a follow-up of 13 years. The placement of the prosthesis is guided by a fluoroscopy and is extracted *via* gastroscopy 4-5 d later. The procedure was performed successfully in all patients, achieving a clinical response of 100% one month after removing the prosthesis and 83.3% in the follow-up of over 10 years. No perforations or mortalities associated with the treatment were reported, with the percentage of migration of the prosthesis at 5%, reflux at 20%, and chest pain at 38.7%. The authors conclude that the use of a temporary self-expanding metallic prosthesis is a safe and effective approach in the treatment of achalasia, with a satisfactory long-term clinical remission rate[76]. In 2010, Cheng *et al*[73] compared the efficacy of different self-expanding metallic prostheses in the long-term treatment of achalasia. They designed a study with 90 patients and separated them into three groups according to the diameter of the prosthesis used (20, 25, and 30 mm). They concluded that the prosthesis with a diameter of 30 mm is associated with a lower incidence of migration and with higher clinical response rates, comparable in the short term with those described for surgical myotomy[73]. The same authors published a prospective randomised study in 120 patients, in which they evaluated the long-term efficacy of a specially designed, partially covered and removable metallic prosthesis, and compared it with PD. They achieved a success rate over 10 years of 83% with the 30-mm prosthesis, while the response rate for the 20-mm prosthesis and PD was 0%[75,77].

Although the results seem promising, they reflect the experience of a single centre, which is why this technique should not be generally recommended. Further randomised studies are required which evaluate its long-term efficacy and safety[75].

Treatment of achalasia with sclerotherapy: Ethanolamine oleate: The injection of a sclerosing agent such as ethanolamine oleate at the level of the LES could be an alternative therapy for patients with refractory achalasia who are not candidates for PD or surgery. Its effect is based on the local inflammatory effect of this substance, but there are still insufficient studies and it is only to be recommended in selected cases[78,79].

THERAPEUTIC MANAGEMENT ALGORITHM

Achalasia therapy is based on achieving the relaxation or mechanical disruption of the LES. Since achalasia is a rare disease, there are few randomised and controlled clinical trials which would enable us to define

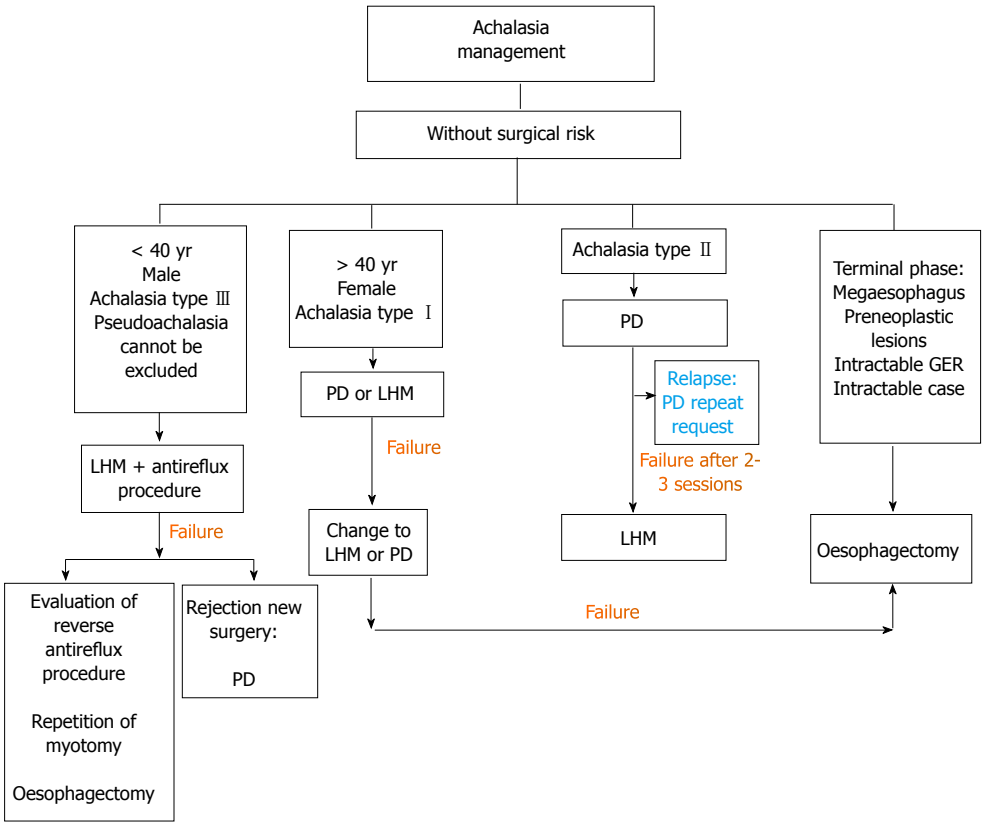

Figure 4 Management algorithm in patients without surgical risk. PD: Pneumatic dilation; LHM: Laparoscopic Heller myotomy.

the optimum strategy. Furthermore, the safety and maintenance of efficacy of the different treatment options vary greatly.

The choice of initial treatment of achalasia is complex and all options are determined by the combination of numerous factors such as the age of the patient, sex, surgical risk, comorbidity, type of achalasia[7], patient preferences, oesophageal anatomical distortion, and the experience of the hospital. Moreover, identifying factors which predict the success of the therapies can inform our recommendations. In Figures 4 and 5, we propose an algorithm for the management of this disease based on the most recent published recommendations[3-5,21,58,80,81]. In general, LHM is the most durable technique in the long term for treating achalasia, however PD is the non-surgical procedure of choice, and it is the most cost-effective strategy. Both techniques are recommended as an initial therapy for treating achalasia in healthy patients who can undergo surgery (Figure 4). The success rate in the short term is comparable for the two techniques.

PD is the most economical non-surgical option, primarily for type Ⅱ. The subtype of achalasia, diagnosed using high-resolution manometry at the beginning of the study, can predict the response of the treatment[58]. Thus we have seen that the success rate with PD is significantly higher for achalasia type Ⅱ (96%) than for type Ⅰ (56%) and type Ⅲ (29%)[82]. The sessions are repeated according to an "on demand" strategy, based on the recurrence of symptoms, and long-term remission can be achieved with it. Criteria for failure include a lack of symptom relief after 2-3 sessions or following the use of the largest diameter balloon chosen. In these cases, the patient must undergo surgery (Figure 4). In high-risk patients, PD can be a reasonable alternative if carried out in hospitals with surgical experience, because of the possibility, however infrequent, of perforation (Figure 5).

Surgical myotomy, using the technique described by Heller a century ago, is the most effective treatment option in the long term[83]. In the last 20 years, this procedure has been carried out safely and successfully using the minimally invasive laparoscopic approach[84], and more recently using robotic assistance. In the majority of cases, it is recommended to also use an anti-reflux fundoplication technique, preferably partial (Dor anterior or Toupet posterior) owing to the fact that it results in significantly lower rates of post-operative dysphagia. It is the procedure of choice in adolescents and young adults, especially male[85], in cases where pseudoachalasia cannot be ruled out and, possibly, in patients with achalasia type Ⅲ (Figure 4)[82], patients with pulmonary symptoms, and those who have not responded to initial treatment with one or two sessions of dilation[37,58,86,87]. The predictors of a poor response after surgery include severe pre-operative dysphagia and preoperative low pressure of the LES (< 30-35 mmHg)[88]. The main predictor of patients

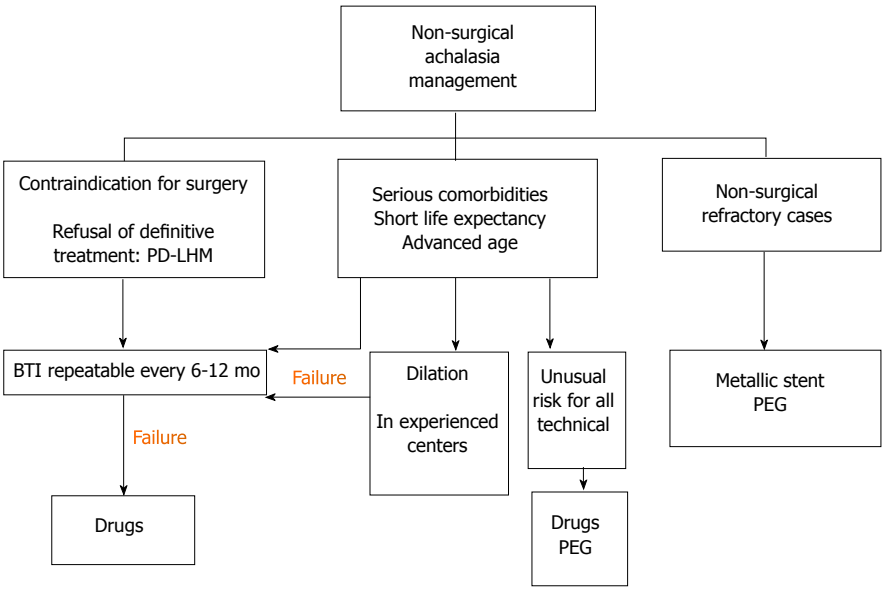

Figure 5 Non-surgical management algorithm. PEG: Percutaneous endoscopic gastrostomy; BTI: Botulinum toxin injection; PD: Pneumatic dilation; LHM: Laparoscopic Heller myotomy.

who will require an additional intervention after the Heller myotomy is an oesophageal dilation of > 6 cm (megaoesophagus) in diameter prior to surgery.

Robotic surgery (Da Vinci® Surgical System, Intuitive Surgical, Mountain View, CA) has been used to treat achalasia as it meets the limitations of conventional laparoscopic surgery, making it more ergonomic for the surgeon and minimally invasive. This involves a computer-assisted surgical device with remote handling. The benefits of amplifying the three-dimensional image enable complex surgical procedures such as fundoplication LMH to be performed more accurately, helping to prevent oesophageal perforation, and to identify residual circular muscle fibres[89].

BTI is the first-line treatment for patients of advanced age, those with severe comorbidities, those with a short life expectancy[16], or those on a waiting list for surgery (Figure 5). It is recommended for patients who are not eligible for more definitive therapies (PD or LHM). Pharmacological treatment with nitrates, calcium channel blockers, and "nitric oxide donors" (sildenafil) may reduce pressure in the LES, but the efficacy is generally unsatisfactory and incomplete. It is recommended for patients who do not want or cannot undergo a more definitive treatment and for whom BTI has failed (Figure 5). Sublingual nifedipine is the most widely used drug. In a review, Cochrane, Wen *et al*[87], identified only two randomised studies evaluating clinical success of nitrates in achalasia and concluded that they cannot give solid recommendations for use. In our experience, it can be a treatment option prior to the extension of the myotomy or the election of oesophagectomy. BTI and medical treatment should only be used in high-risk patients (Figure 5), and as an intermediate step prior to other, more durable treatments[3].

POEM is a new treatment[90] which has shown good results in the short term, including following a myotomy with anterior fundoplication[91]. It is profiled as a viable option for patients following the failure of a myotomy, in the absence of more controlled studies, long-term results, and comparison with current techniques.

Despite the improvement in symptoms offered by PD and LHM, 10%-15% will present progressive deterioration of the oesophageal function, and up to 5% may require an oesophagectomy in the terminal stage when they do not respond to any treatment (Figure 4)[92]. The ideal method of reconstruction following oesophagectomy has not yet been established, the options being gastric, colonic, or jejunal[3]. The treatment option for refractory achalasia is (Figure 5)[93] the minimally invasive Ivor-Lewis oesophagectomy. The success rate is close to 90%, although there is a significant risk of respiratory complications, anastomotic strictures, and leaks, dumping syndrome, regurgitation, and bleeding. The placement of percutaneous endoscopic gastrostomy (PEG) can be considered a suitable alternative in patients with an unusually high risk for other techniques. However, it does not tend to reduce the symptoms or risks of aspiration of salivary retention.

ROLE OF ENDOSCOPY IN THE DIAGNOSTIC THERAPEUTIC PROTOCOL OF ACHALASIA

Evaluation to guide treatment

The success of the treatment must be documented using objective parameters. Since there are deficiencies in the correlation between the latter and clinical symptoms, an adequate strategy includes periodic monitoring to detect symptomatic recurrences at an early stage. The symptoms can also reappear due to an initial incomplete myotomy, the growth of new muscular

fibres, or stenosis. The first clinical evaluation should be performed at an early stage (1-3 mo) after the initial intervention, and every 1-2 years thereafter[88]. The most widely used system for scoring symptoms is the Eckardt score[94]. The Eckardt score (maximum score, 12) is the sum of the symptom scores for dysphagia, regurgitation, and chest pain (0, absent; 1, occasional; 2, daily; and 3, each meal), and weight loss (0, no weight loss; 1, < 5 kg; 2, 5-10 kg; and 3, > 10 kg). This register allows new explorations, barium oesophagram, and EGD to be indicated. In addition, regular monitoring is important not only to ensure clinical control, but also to decide on the need for retreatment and to prevent complications at a later stage. Regardless of the subtype of achalasia, the long-term positive response variable most widely used in Europe is post-treatment LES pressure < 10 mmHg[24,88,95]. Other centres use the timed measurement of the barium column after the PD as a predictor of success. In this respect, a decrease by > 50% with respect to the basal pressure within 1 min is associated with a clinical improvement[41,96]. Some institutions perform oesophageal manometry intraoperatively or immediately after the dilation[97,98]. However, the pressure of the LES could be falsely raised as a result of oedema or intramural haematoma following the intervention. There is a new method for the intraoperative evaluation of the diameter of the EGJ (EndoFLIP). It is an endoluminal probe, which produces functional images of the diameter of the EGJ in real time using impedance planimetry. However, more studies are needed to determine the best parameter for retreatment[99]. There is no treatment for the neural lesion considered to be responsible for achalasia, which is why oesophageal peristalsis is rarely normalised following any of the therapies. However, some cases have been described in which recovery of peristalsis occurs, both following myotomy and following dilation[100-104]. Different authors have associated this with close monitoring of patients and the early indication of treatment, thus avoiding progression to advanced stages with oesophageal atony.

Endoscopic surveillance of complications

The primary role of endoscopy is to detect, prevent, and treat immediate and long-term complications deriving from the disease itself and the therapies applied. Endoscopy immediately after an endoscopic intervention is only indicated for the treatment of complications arising from the techniques used. However, there are currently no guidelines for monitoring squamous cell carcinoma or other late complications such as oesophageal and peptic stenosis, or megaoesophagus. More data are needed to determine which follow-up guidelines will improve the overall result in this disease, since prospective monitoring studies over > 30 years have shown a benefit in long-term survival in only 13% of cases[105].

The most prevalent complications in the long term when the treatment has been effective are mainly due to GER, which occurs in almost 25% of patients after a follow-up of > 15 years[106]. Following PD, the symptoms are generally relieved and temporary, and can be easily controlled with PPI. However, more severe complications have been described following surgery, including the incidence of reflux symptoms of 18% (range 5%-55%)[49]. These complications can be markedly reduced by adding a Dor fundoplication to the LHM[107]. The second most frequent complication is the progressive dilation of the oesophagus which leads to sigmoid megaoesophagus, and appears in 10% of cases of > 10 years of progression[88]. The most feared complication is oesophageal cancer, the prevalence of which ranges from 0.4%-9.2%, squamous cell cancer being more frequent[108-111] than Barrett's adenocarcinoma (associated with GER after myotomy). In this case, and although more studies are required, the majority of experts, including the latest guidelines from the American Society of Gastrointestinal Endoscopy[112], advocate some form of endoscopic surveillance 15 years after the initial diagnosis, and in patients with oesophageal stasis[5,113], but the subsequent monitoring interval has not been defined.

CONCLUSION

Achalasia is a primary oesophageal disorder for which there is no curative treatment. Pneumatic dilation and surgical myotomy are recommended initial therapies in healthy patients because they offer the best results in the long term. Botulinum toxin injection and medical treatment have transitory effects, and should be reserved for high-risk patients or as an intermediate measure before more definitive treatment. Other new options without definitive location in the therapeutic algorithm are peroral endoscopic myotomy, metallic stents, and ethanolamine injection. In refractory cases and in terminal stages, oesophagectomy is an option. Follow-up after the treatment is indicated to detect recurrences, indicate retreatment, and prevent late complications.

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REVIEW

Endoscopic management of biliary complications after liver transplantation: An evidence-based review

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Abstract

Biliary tract diseases are the most common complications following liver transplantation (LT) and usually include biliary leaks, strictures, and stone disease. Compared to deceased donor liver transplantation in adults, living donor liver transplantation is plagued by a higher rate of biliary complications. These may be promoted by multiple risk factors related to recipient, graft, operative factors and post-operative course. Magnetic resonance cholangiopancreatography is the first-choice examination when a biliary complication is suspected following LT, in order to diagnose and to plan the optimal therapy; its limitations include a low sensitivity for the detection of biliary sludge. For treating anastomotic strictures, balloon dilatation complemented with the temporary placement of multiple simultaneous plastic stents has become the standard of care and results in stricture resolution with no relapse in > 90% of cases. Temporary placement of fully covered self-expanding metal stents (FCSEMSs) has not been demonstrated to be superior (except in a pilot randomized controlled trial that used a special design of FCSEMSs), mostly because of the high migration rate of current FCSEMSs models. The endoscopic approach of non-anastomotic strictures is technically more difficult than that of anastomotic strictures due to the intrahepatic and/or hilar location of strictures, and the results are less satisfactory. For treating biliary leaks, biliary sphincterotomy and transpapillary stenting is the standard approach and results in leak resolution in more than 85% of patients. Deep enteroscopy is a rapidly evolving technique that has allowed successful treatment of patients who were not previously amenable to endoscopic therapy. As a result, the percutaneous and surgical approaches are currently required in a minority of patients.

Key words: Biliary stricture; Bile leakage; Liver transplantation; Endoscopic retrograde cholangio-pancreatography; Plastic stents; Fully-covered self-expandable metal stents

Core tip: One third of liver transplant recipients are

affected by biliary tract complications which are the major source of morbidity in these patients. Biliary-biliary (as opposed to bilio-enteric) anastomoses are first treated by endoscopy, with resolution of > 85% and > 75% of cases in deceased and living-donor transplant recipients, respectively. New stenting protocols and new designs of fully covered self-expandable metal stents are at the frontline of efforts aiming to reduce patient burden during treatment. Here, we discuss the latest developments in the endoscopic approaches to these complications.

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INTRODUCTION

Liver transplantation (LT) has become a standard of care in patients with end-stage liver disease. After LT, approximately one third of patients are affected by biliary tract complications and these result in significant morbidity and decreased patient survival[1]. Due to the scarcity of organ donors and the increasing number of patients waiting for LT, living donor liver transplantation (LDLT) has emerged as an alternative to deceased donor liver transplantation (DDLT). Even though surgical techniques are constantly improving, biliary complications are more frequent following LDLT compared with DDLT[2]; LDLT also remains characterized by its technical complexity and ethical controversies.

Biliary complications following LT include biliary leaks, strictures, choledocholithiasis and other less common conditions[3,4]. Approaches commonly used for treating biliary complications involve endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC) and surgery. ERCP is commonly regarded as the first choice treatment modality in most circumstances; if it fails PTC is often used, reserving surgery for severe complications or refractory conditions not manageable by less invasive techniques[5-8].

Here we review the literature focusing on the endoscopic management of biliary complications, the different strategies for treating strictures and biliary leaks and summarize their outcomes.

ETIOLOGY, RISK FACTORS AND DIAGNOSIS

Biliary reconstruction in LT

It is essential for endoscopists to have a clear comprehension of the different types of surgical reconstruction during LT. Biliary reconstruction is performed at the end of LT, once all vascular anastomoses have been completed. An end-to-end choledoco-choledocal anastomosis is the first choice procedure in most institutions following whole organ LT in patients with healthy native bile ducts of suitable caliber[6,9]. This technique produces physiological bilioenteric continuity, preserves the function of the sphincter of Oddi and allows for potential future endoscopic treatment of biliary complications. Bilioenteric reconstruction (Roux-en-Y hepaticojejunostomy) is performed in cases of previous biliary tract disease (*e.g.*, sclerosing cholangitis, biliary atresia), large disparity in size or small caliber of the bile ducts, and may be preferred in cases of retransplantation because of inadequate recipient duct length[10]. Due to the shortage of cadaveric livers, LDLT has gained popularity in adult patients. With LDLT, the living donor's right or left lobe or the left lateral segment is transplanted. Ductal anastomoses are more difficult to perform than in DDLT due to the small caliber of the intrahepatic ducts. In reduced size split-liver transplantation, a liver from a dead donor is splitted into two organs to permit two recipients to receive a graft; the anastomoses of both right and left lobe are alike to those of LDLT.

Risk factors for biliary complications

Biliary complications may be promoted by multiple risk factors related to recipient, graft, operative factors and post-operative course: (1) among recipient-related factors, advanced recipient age and more advanced liver function impairment contribute to the development of biliary complications[11,12]; (2) among graft-related factors, prolonged cold and warm ischemia time, extended donor criteria grafts and donation after cardiac death, as opposed to brain death, are associated with a higher incidence of ischemic-type biliary lesions (ITBL)[13,14]. Nonetheless, a recent report by Vanatta *et al*[15] showed that, by carefully selecting donors and recipients, overall patient and graft survival as well as the incidence of ITBL were similar following donation after cardiac *vs* brain death[15]; (3) operative risk factors are different for DDLT and LDLT for various reasons: LDLT by itself is an important risk factor for biliary complications due to the small duct size, the presence of multiple biliary duct outlets and the devascularization of the bile ducts during hilar dissection of the graft[16-18]. In DDLT, T-tube placement for duct to duct (DD) reconstruction allows minimizing the incidence of anastomotic strictures[19] and it is unequivocally recommended by some authors[20]; however, this results in biliary leakage following T-tube removal in 5%-33% of cases[19]; (4) during the postoperative course, early hepatic artery thrombosis may lead to the severest forms of non-anastomotic strictures, at multiple sites of the donor biliary system, because blood supply to the bile ducts is fragile. This may result in partial or total biliary necrosis with the formation of typical biliary casts and multiple intraluminal filling defects at

cholangiography[5,21]; and (5) other documented factors, including ABO incompatibility, cytomegalovirus infection and chronic/acute rejection episodes have been reported to be potential risk factors for biliary complications in historical publications; more recently these factors have been strongly associated with non-anastomotic, rather than anastomotic, complications[22-24].

Diagnostic approach

The clinical presentation of biliary complications varies considerably; patients could present no symptom at all, jaundice, abdominal pain, biliary leak or cholangitis. In asymptomatic LT recipients, a biliary complication usually is first suspected because of elevations of serum bilirubin, alkaline phosphatase, and/or gamma-glutamyl transferase levels. In the case of cholestasis, the initial diagnostic step is to discriminate obstructive *vs* nonobstructive causes, like LT rejection (acute or chronic), recurrence of primary disease and drug-induced cholestasis.

The initial evaluation should include a liver ultrasound (US) with a Doppler evaluation of the hepatic vessels, due to the frequent association of biliary complications with the presence of hepatic artery thrombosis or stenosis[6,25]. If hepatic artery stenosis or occlusion is suspected by Doppler US, multidetector computed tomography should be used as the second-line modality of choice for the rapid assessment of major vascular complications requiring pre-treatment confirmation. If hepatic artery thrombosis is confirmed, angiographic intervention should be performed urgently to re-establish hepatic artery flow[26,27]. Magnetic resonance cholangiopancreatography (MRCP) has substantially facilitated the accurate recognition of biliary tract complications (sensitivity and specificity of 93%-97% and 92%-98%, respectively, compared with ERCP as the reference standard)[28-31]. MRCP provides the endoscopist with a map of the whole biliary tract and, unlike ERCP, consistently demonstrates ducts even upstream from a tight stricture, therefore it is especially useful for hilar or intrahepatic anastomotic strictures. When findings at MRCP were compared to other approaches, including ERCP, PTC, and surgery to diagnose post-LT biliary complications, the sensitivity, specificity, positive predictive value, and negative predictive of MRCP were 98%, 94%, 94%, and 98%, respectively[31]. Its main disadvantages include a low sensitivity in the case of sludge or small stones (< 5 mm). MRCP is noninvasive and is the technique of choice for diagnosing post-LT biliary complications.

Etiology and types of biliary strictures

Post-LT biliary strictures are usually classified as anastomotic strictures (ASs) or non-anastomotic strictures (NASs), also called ischemic type biliary strictures (ITBS)[32-34]. Biliary strictures complicate around 2%-14% of LT and can be categorized in to early or late (occurring within or after the first month following LT, respectively). Strictures which appear soon after LT are commonly referable to technical problems, whereas late strictures are generally attributable to vascular insufficiency and problems with healing and fibrosis. In a recent systematic review, 1844 (12.8%) of 14359 LT patients had biliary strictures. The appearance of a stricture varies widely, from 7 d to 11 years after LT[35].

Anastomotic strictures: ASs can present at any time after transplantation but most of them are diagnosed within one year following LT with a mean interval between LT and diagnosis of 5-8 mo. ASs complicate around 6%-12% and 34% of deceased and living donor LT procedures, respectively[33,36,37]. ASs pathogenesis is believed to include inadequate mucosa-to-mucosa anastomosis, local tissue ischemia, and the fibrotic nature of the healing process[33,38]. ASs are solitary and short in length (Figure 1A and B). They may involve a choledocho-jejunostomy or a choledocho-choledochostomy; they are considered clinically relevant only if cholestasis or cholangitis are present. A slight and transient narrowing of the biliary lumen occurs frequently within the first one to two months following biliary anastomosis due to postoperative edema and inflammation, but it is uncertain how many of these cases progress to clinically significant ASs (Figure 1A)[33]. ASs can generally be effectively treated by endoscopic means and do not decrease graft or patient survival.

Non-anastomotic strictures: Post-LT strictures are classified as NASs if they are located more than 5 mm proximal to the anastomosis (Figure 1D). They account for 10% to 25% of all strictures complicating LT, with an incidence in the range of 0.5% to 10%[19,38-40]. NASs are considered to derive from ischemic damage to the duct as it may occur following hepatic artery thrombosis. Conditions associated with NASs include a prolonged ischemia time (cold and warm), transplantation after cardiac death donation, prolonged vasopressor support for the donor, ABO-type incompatibility, primary sclerosing cholangitis, autoimmune hepatitis or hepatitis C virus infection in the recipient[41-48]. Furthermore, nowadays a wider acceptance of older and extended criteria donors has been suggested to contribute to an increased incidence of NASs[19]. True NASs, usually referred to as ITBSs, characteristically are diffuse and include the hilum and sectorial or segmental intrahepatic branches. The treatment of NASs is technically more difficult than that of ASs and, in the case of hepatic artery thrombosis, the endoscopic treatment is mostly ineffective if the arterial blood flow cannot be restored.

Etiology and types of biliary leaks

Biliary leakage is the second most common complication after LT, with an incidence of 2%-21%[19,49,50]. In a recent meta-analysis, the rate of biliary leakage after LT

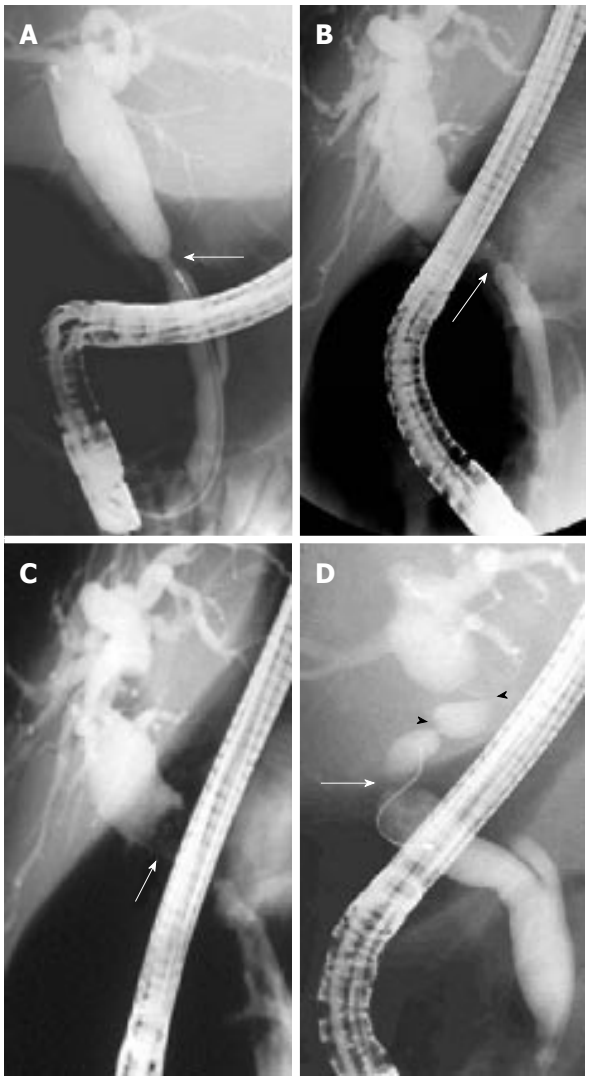

Figure 1 Biliary strictures at endoscopic retrograde cholangiopancreatography. A: Early and incipient anastomotic stricture (arrow) with upstream biliary dilation; B and C: Late and high-grade anastomotic stricture (arrow) > 1 year after deceased-donor liver transplantation, with a large stone located upstream from the stricture (arrow); D: Combination of anastomotic (arrow) and non-anastomotic (arrow heads) strictures.

was 8.2%, without significant difference between DDLT (7.8%) and LDLT (9.5%)[35]. Leakage may develop at the level of the anastomotic site, from the cystic duct remnant, from the cut surface of partial liver grafts in the case of LDLT, and following T-tube removal (Figure 2). Bile leaks can be classified into two categories: early bile leaks, which present within 4 wk following LT (these usually occur at the anastomotic site and are often related to technical issues, not to the type of biliary reconstruction), and late bile leaks, which present beyond this time (they are usually related to T-tube removal, resulting from delayed T-tube tract maturation possibly related to immunosuppression). A bile leak should be suspected in any patient who develops abdominal pain, fever or any sign of peritonitis following LT, especially after T-tube removal. Bile leaks can derive in collections of fluids and abscesses that might be related to strictured or disconnected ducts. Depending on the size of the leakage and the clinical presentation, bile leaks can be managed conservatively, nonsurgically or surgically[4,51].

Etiology and type of intraluminal biliary filling defects

Stones, sludge and casts occur in approximately 5% of patients after LT, with stones accounting for 70% of the cases. Biliary stone disease is associated with disorders that can reduce the flow of bile such as ASs or NASs. In addition, medications such as cyclosporine may play a role in bile lithogenicity by inhibiting bile secretion and promoting functional biliary stasis. Sludge is described as a thick collection of mucus, calcium bicarbonate and cholesterol crystals, which, when left untreated, can transform into biliary stones (Figure 3A).

Casts refer to the presence of multiple hard pigmented dark material that mold the bile ducts (Figure 4). These are thought to develop due to bile duct mucosal damage related to obstruction, ischemia, or bacterial infection. A history of hepatic artery thrombosis and a prolonged cold ischemia time are associated with debris formation[52-54]. This disorder occurs in 2.5% to 18.0% of LT recipients[32,54]. Casts are associated with increased morbidity, graft failure, retransplantation and mortality.

Sphincter of oddi dysfunction

Sphincter of oddi dysfunction (SOD) describes a clinical syndrome of biliary or pancreatic functional obstruction that may be responsible for cholestasis, pain, or pancreatitis.

It is hypothesized that, in the post-LT setting, denervation of the ampulla (secondary to surgical intervention) might generate a hypertonic sphincter, resulting in increased intraductal biliary pressure. This complication has been reported in 2% to 7% of patients who have undergone LT[55,56]. Typically, patients present with cholestasis, dilation of the distal bile duct and no obstacle detected at cholangiography.

ENDOSCOPIC MANAGEMENT

Managing post-LT biliary complications needs a multidisciplinary team involving transplant surgeons, hepatologists, endoscopists, and interventional radiologists. Endoscopic therapy is the first line therapy in most cases with a duct-to-duct anastomosis. With recent developments in enteroscopy, many patients with Roux-en-Y hepaticojejunostomy can also be treated endoscopically[57], with PTC being mostly reserved for the salvage of failures. The spectrum of endoscopic therapies includes biliary sphincterotomy, balloon dilation of strictures, basket and balloon extraction of stones, sludge, and casts, and the placement of one or multiple, side-by-side, biliary plastics stents. Additionally, cholangioscopy allows the characterization of strictures by observation and tissue sampling, and therapy of difficult casts or stones by intraductal lithotripsy[58-62]. Endoscopic therapy is usually highly successful and has a low incidence of procedure-related complications,

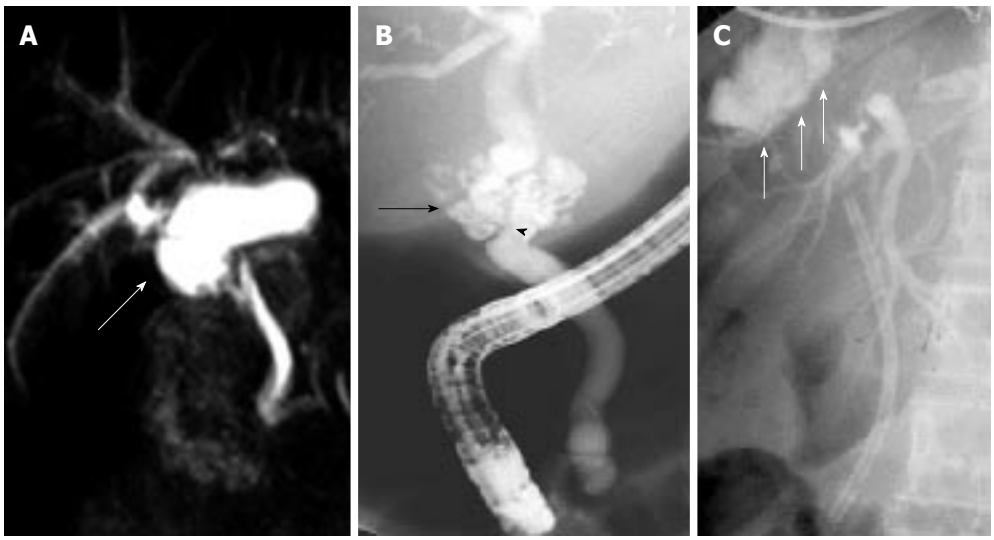

Figure 2 Biliary leaks. A: Biloma (arrow) resulting from anastomotic leakage early after liver transplantation as shown at magnetic resonance cholangiopancreatography; B: Anastomotic leakage (arrow) at the level of an anastomotic stricture (arrow head) early after liver transplantation as shown at endoscopic retrograde cholangiopancreatography (ERCP); C: Multiple leak sites from the cut surface in a split liver transplantation patient (arrows) as shown at ERCP with a plastic biliary stent in place.

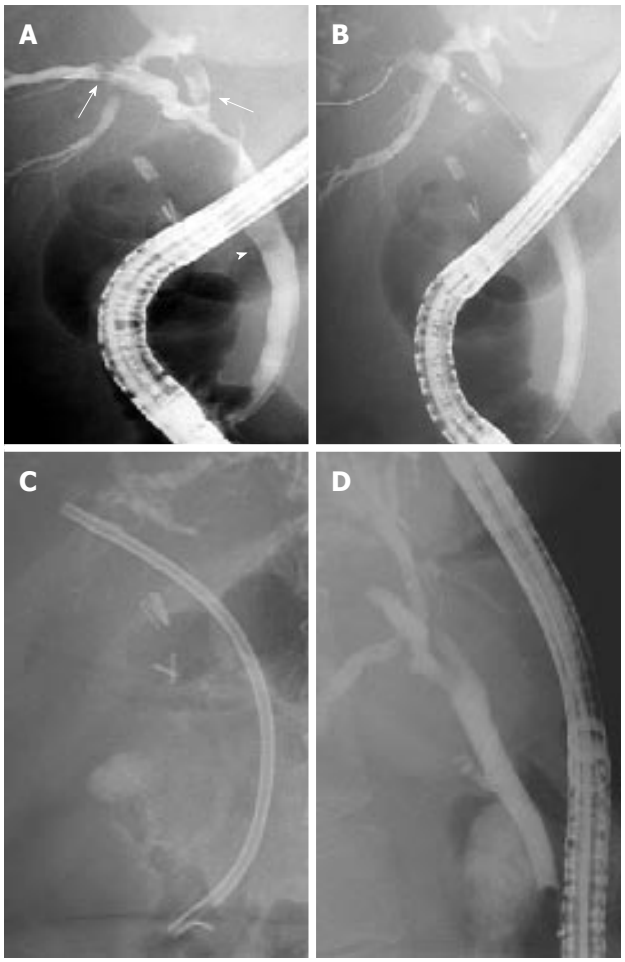

Figure 3 Endoscopic treatment of an anastomotic biliary stricture with upstream sludge and downstream stone after living donor liver transplantation. A: Anastomotic biliary stricture with upstream sludge (arrows) and downstream stone (arrowhead); B: Stricture dilation using a 10-mm in-diameter balloon; C: 10-F plastic biliary stent in place; D: Absence of residual stricture at late follow-up.

reserving surgery as a last option intervention if endoscopic and/or percutaneous treatment is not feasible or is ineffective.

Biliary leaks

Traditionally, post-LT biliary leaks have been treated surgically with anastomotic revision or conversion to a Roux-en-Y hepaticojejunostomy if a duct-to-duct anastomosis is not technically feasible. With advances in endoscopic therapy, ERCP has now become the initial therapeutic option in the management of biliary leaks. Usually the leakage of bile is treated through biliary sphincterotomy followed by the placement of a transpapillary stent (Figure 2C) for 2 to 3 mo (in contrast to post-cholecystectomy leaks, where the stent can be removed in 4 to 6 wk) with the aim of ensuring the proper healing of the leaks. Prolonged stenting is advised because healing may be delayed by immunosuppressors. If the leak is associated with a biliary stricture, this can be prudently dilated before inserting one or more plastic stents upstream from both the stricture and the leak[63]. Biliary stenting provides faster leak resolution than sphincterotomy alone and it is equally effective whether sphincterotomy is performed or not. At the time of stent removal, a careful anatomical evaluation should be performed and duct cleansing should always be performed because biliary abnormalities (mostly sludge, stones, or persistent leak) can be found at this time in a significant proportion of patients[64]. Endoscopic therapy solves the leakage of bile in more than 85% of patients[38,63-66]. Recently, fully covered self-expandable metal stents (FCSEMS) have been used in a pilot study of 17 LT recipients with biliary leaks[67]. FCSEMS offered minimally invasive and low-morbidity short-term control of leaks but it resulted in a relatively high stricture rate. In this series of 17

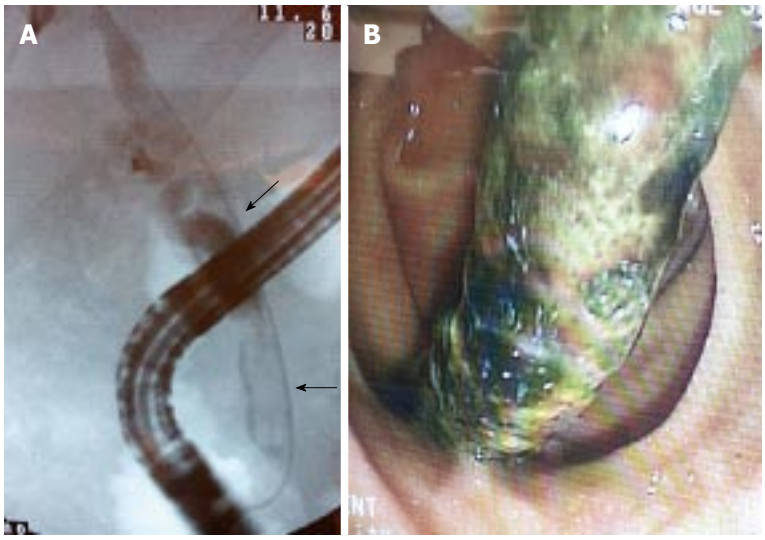

Figure 4 Elongated intraductal filling defects in the choledocus and common hepatic duct suggestive of biliary casts (arrows) (A) and endoscopic view of the successfully removed cast (B).

patients, 8 (47%) patients developed common bile duct strictures following FCSEMS removal; of these, 6 (35%) required repeat endoscopic treatment for a clinically significant stricture, therefore the use of current FCSEMS models cannot be recommended in the post-LT population. In specific situations, endoscopic therapy can be impossible or fail, for example, in the case of large anastomotic leaks associated with hepatic artery compromise or surgically altered anatomy (Roux-en-Y anastomosis). These patients will most often require surgical management.

Biliary strictures

Anastomotic strictures: No standard protocol has emerged for the endoscopic therapy of ASs. By analogy with the more frequent postcholecystectomy biliary stricture, endoscopic therapy of ASs usually requires biliary sphincterotomy plus balloon dilatation (BD) and stent placement (Figure 5). The use of BD alone in early onset anastomotic strictures (the first 2 mo following LT) may be effective. However, despite good initial success, BD alone led to a high rate of recurrent stricture formation[68]. Therefore, the combination of BD and stenting is a more adequate approach[33,65,68-71].

Multiple 10-Fr plastic stents are usually maintained until stricture resolution or for a minimum of 12 mo, with stent exchange scheduled every 3-4 mo to reduce the chance of stent blockage and cholangitis. In a recent systematic review that included 440 LT-related ASs treated with multiple simultaneous plastic stents[72], the mean AS resolution rate was approximately 85% for early as well as late ASs. Higher ASs resolution rates (97% *vs* 78%) and lower ASs recurrence rates (1.5% *vs* 14%) have been reported with stenting durations > 12 mo *vs* < 12 mo. This was observed despite the fact that shorter stenting durations were applied for early *vs* late ASs. Most cases of ASs recurrence were successfully managed with repeat plastic stenting.

Recently, different strategies of AS treatment have been described to decrease patient burden: (1) long-term maximal stent therapy with stent exchange only when signs or symptoms of biliary obstruction are detected: this strategy has allowed minimizing the number of ERCPs needed to treat ASs without compromising success or patient safety. With this protocol, complete AS resolution was reached in 94% of patients and recurrence rate at a median follow-up of 11 mo was 3%[73]. The authors reported in a total of 83 patients 2 cases of post-ERCP pancreatitis, 2 cases of periprocedural bacteremia but no episodes of cholangitis caused by stent occlusion; (2) stent exchange every 2 wk: ERCP with rapid-sequence balloon dilation followed by stenting with multiple stents over a short time period[74]. With this approach, mean stenting duration was 107 d and long-term stricture resolution was achieved in 33 (87%) of 38 patients; ERCP-related complications occurred in 2 (5%) patients. During a mean follow-up of one year after stent removal, 5 (13%) patients had a stricture recurrence, successfully retreated by endoscopic means in 4 cases; and (3) temporary placement of covered self-expandable metal stent (SEMSs). Covered SEMSs offer the advantage of longer stent patency and larger nominal diameter compared with a single plastic stent. Covered SEMSs should be maintained in place for a minimum of 3 mo as shorter stenting durations result in lower ASs resolution (72% *vs* 90%)[75-79]. In the systematic review cited above[72], covered SEMSs had a much higher stent migration rate (16%) compared with simultaneous multiple plastic stenting. Furthermore, covered SEMS carry a low but real risk of tissue ingrowth and stent impaction. Therefore, the authors concluded that current evidence does not suggest a clear advantage of SEMS use over multiple simultaneous plastic stenting in the management of ASs. In a large prospective study that was not included in the systematic review[80], the AS resolution rate using FCSEMSs was 68% of 42 LT patients and the migration rate was 17% and 75% at 3 and 6 mo, respectively. In this study, cholangitis was reported in 24% of patients with LT-related ASs and it

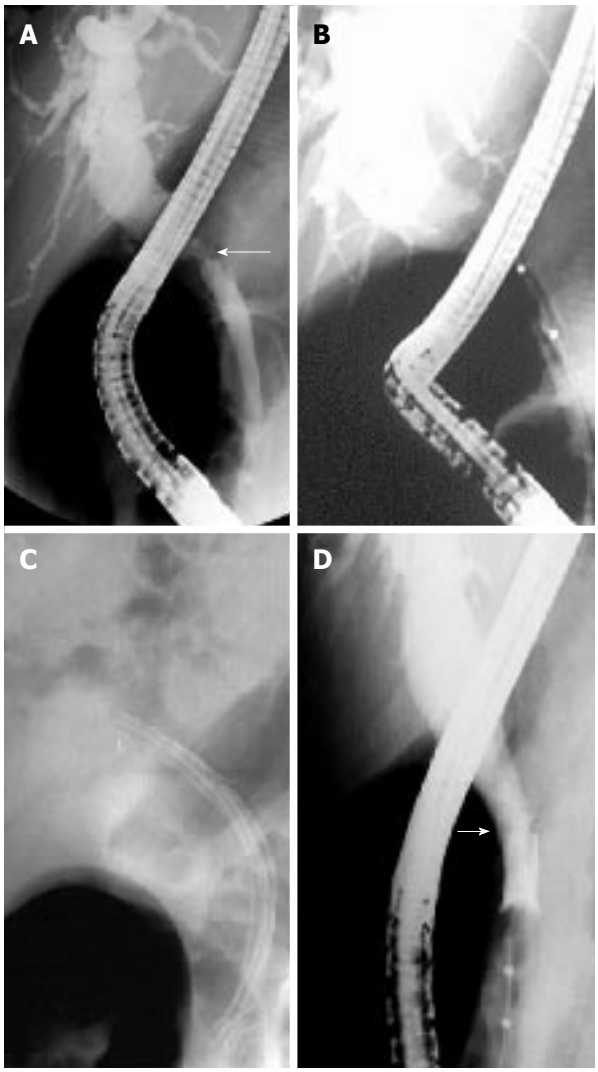

Figure 5 Endoscopic treatment of an anastomotic biliary stricture after deceased donor liver transplantation. A: Late, high-grade, anastomotic stricture (arrow) with a stone partially concealed by the endoscope; B: Stricture dilatation with a 4-mm in-diameter balloon; C: Three 10-Fr plastic stents in place, no residual stone; D: Balloon occlusion cholangiogram showing stricture disappearance at the end of treatment (arrow).

was strikingly associated with stent migration. Finally, a recent randomized trial compared a new design of FCSEMS *vs* multiple simultaneous plastic stenting in 20 patients with LT-related ASs[81]. ASs resolution rates were similar with both stent models but complication rate and hospital stay duration were non-significantly higher with the plastic stent *vs* FCSEMS, suggesting that some FCSEMS designs that effectively prevent stent migration might be a cost-effective alternative to plastic stenting.

Endoscopic management of ASs seemed to be more challenging in LDLT *vs* DDLT due to the complexity of duct-to-duct anastomosis. However, using an aggressive strategy of maximal endoscopic stent placement, two studies reported high (75%-100%) AS resolution rates in LDLT patients[82,83]. The long-term resolution rates of biliary leaks and/or strictures reported in selected retrospective studies are summarized in Table 1[37,82-87].

Table 1 Retrospectives series showing living donor liver transplantation endoscopic anastomotic strictures treatment results

Ref.	Patients (*n*)	Stenting (m)	Success (%)	F/U (m)	Relapse (%)
Yazumi *et al*[37] (2006)[1]	75	6	68	20 (1-50)	10
Gómez *et al*[84] (2009)	10	NR	20	30.5 (2-23)	NR
Seo *et al*[87] (2009)	29	3-6	64.5	31	30
Chang *et al*[86] (2010)	113	3-6	26.5	33 (3-96)	NR
Kim *et al*[85] (2011)	112	12.7	36	42.8 ± 15.2	11.5
Chan[82] (2013)	8	NR	75	18 ± 8.7	NR
Hsieh[83] (2013)[2]	38	5.3	100	74	21

[1]Combination of percutaneous transhepatic biliary drainage plus endoscopic retrograde cholangiopancreatography (ERCP) in 9 patients and inside stents technique; [2]Combination of percutaneous transhepatic biliary drainage plus ERCP in 6 patients. NR: Not reported.

Factors identified as independent predictors of failed endoscopic treatment of LDLT-related ASs include higher LT recipient age, longer operation duration, and a pouched morphology of the AS[84,88]. Recurrent ASs occur in approximately 21% of patients and may be retreated by endoscopy[83]. PTC plays an important role when a guide wire cannot be inserted through the anastomotic stricture at the time of ERCP (*e.g.*, disconnected duct, some refractory angulated or twisted strictures). For these patients, the rendez-vous technique (PTC + ERCP) may be useful to insert a stent above the stricture. This approach has been demonstrated to be feasible and relatively safe for the management of biliary strictures complicating LDLT with duct-to-duct anastomosis[89]. The endoscopic treatment of some ASs can be unsuccessful and may need long-term stenting or surgical hepaticojejunal anastomosis[87,90].

Non-anastomotic strictures: The endoscopic therapy of NASs or ITBSs often involves the hilum and intrahepatic ducts and is notably more demanding than the therapy of ASs. The stenosis at the level of the sectorial or segmental branch ducts can result in a cholangiographic appearance that simulates primary sclerosing cholangitis. It is challenging to make general recommendations for managing NASs and treatment should be individualized. Treatment success depends upon stricture grade, number, and location. Extra-hepatic strictures generally respond better to therapy and altogether, in the few published reports of endoscopic treatment, the success rates ranged between 50% and 70%[50,91]. Finally, a few patients (especially the ones with complex ischemic intrahepatic strictures) may need surgical revision or retransplantation.

In patients who have undergone Roux-en-Y hepaticojejunostomy, a potential alternative to PTC is the use of various techniques of enteroscopy. In 25 pediatric patients with hepaticojejunal anastomoses, the bilioen-

teric anastomosis could be reached in 17 patients, a stent could be placed in 9 patients and AS resolution was obtained in 5 (20%) patients, showing the difficulty of this procedure[92]. In a series of 44 adults with choledochojejunal AS following various hepato-biliary-pancreatic surgery, temporary stenting (including stent removal) was achieved in 32 (73%) patients and restenosis occurred in 7/32 patients[93].

Other complications

Biliary stones, sludge and casts: In LT recipients, the endoscopic management of stones is similar to that performed in the nontransplant setting although the approach may be complicated by the presence of a stricture downstream from the stone. In such circumstances, delayed stone extraction (following biliary stenting) or advanced endoscopic techniques like intraductal lithotripsy or direct choledocoscopy may be required to achieve stone removal. In patients with serious coagulation disorders or thrombocytopenia where sphincter ablation may be relatively contraindicated, balloon dilatation of the intact sphincter can be applied.

For biliary casts, the endoscopic approaches are alike to those utilized in stone disease. However, the success rate is significantly lower owing to the multiplicity of filling defects located in intrahepatic bile ducts[39]. Treatment usually requires multiple ERCPs, possibly complemented with PTC and it may require retransplantation in a significant proportion of cases[39,94] Cholangioscopy might aid to discriminate biliary casts from strictures[59].

Sphincter of Oddi dysfunction and papillary stenosis

As for SOD in the non-LT setting, biliary sphincterotomy is the common treatment and provides a high success rate[39]. The question of whether these patients are at similar risk of post-ERCP pancreatitis as those who are affected in the non-LT setting has not been formally studied; however it seems reasonable to consider prophylactic pancreatic stenting in addition to standard rectal administration of NSAIDs when performing sphincterotomy in these patients[95].

SUMMARY

Biliary complications remain a burden in LT patients and continue in some cases to be a challenging aspect of the multidisciplinary care of LT patients. As biliary complications are the most frequent complication following LT, the index of suspicion for requesting further investigations should be low. MRCP is the most useful examination to establish the diagnosis, especially because the low sensitivity of US may be more detrimental in LT as compared to the average patient. Successful endoscopic treatment is achieved in most cases, with the notable exceptions of ASs in LDLT patients, NASs and biliary casts. For ASs, temporary simultaneous multiple plastic stenting for a minimum of 12 mo (except in some cases of early AS) remains the standard of care; FCSEMS have yielded disappointing results up to now. In patients with choledocojejunostomy, deep enteroscopy techniques may allow successful treatment but success rates are lower. Nowadays PTC and surgery are reserved for a small minority of patients.

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REVIEW

Review of diagnostic and therapeutic endoscopic retrograde cholangiopancreatography using several endoscopic methods in patients with surgically altered gastrointestinal anatomy

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Abstract

The endoscopic approach for biliary diseases in patients with surgically altered gastrointestinal anatomy (SAGA) had been generally deemed impractical. However, it was radically made feasible by the introduction of double balloon endoscopy (DBE) that was originally developed for diagnosis and treatments for small-bowel diseases. Followed by the subsequent development of single-balloon endoscopy (SBE) and spiral endoscopy (SE), interventions using several endoscopes for biliary disease in patients with SAGA widely gained an acceptance as a new modality. Many studies have been made on this new technique. Yet, some problems are to be solved. For instance, the mutual unavailability among devices due to different working lengths and channels, and unestablished standardization of procedural techniques can be raised. Additionally, in an attempt to standardize endoscopic procedures, it is important to evaluate biliary cannulating methods by case with existence of papilla or not. A full comprehension of the features of respective scope types is also required. However there are not many papers written as a review. In our manuscript, we would like to evaluate and make a review of the present status of diagnostic and therapeutic endoscopic retrograde cholangiopancreatography applying DBE, SBE and SE for biliary diseases in patients with SAGA for establishment of these modalities as a new technology and further improvement of the scopes and devices.

Key words: Double balloon endoscopy; Single balloon endoscopy; Spiral endoscopy; Endoscopic retrograde cholangiopancreatography; Roux-en-Y reconstruction

Core tip: This study is a review of the status of diagnostic and therapeutic endoscopic retrograde cholangiopancreatography using several endoscopic methods in patients with surgically altered gastrointestinal

anatomy, evaluating the results from multiple centers over the world. The descriptions of features of the respective endoscopes including the introduction of new endoscopes are summarized. Assessment of the procedures is concretely made by type of reconstruction methods and by type of applied endoscopes, which suggests the present and future challenges to be overcome.

Shimatani M, Takaoka M, Tokuhara M, Miyoshi H, Ikeura T, Okazaki K. Review of diagnostic and therapeutic endoscopic retrograde cholangiopancreatography using several endoscopic methods in patients with surgically altered gastrointestinal anatomy. *World J Gastrointest Endosc* 2015; 7(6): 617-627 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i6/617.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i6.617

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is now one of the most effective diagnostic and therapeutic modalities in patients with biliary diseases. The success rate is > 90% for patients with normal anatomy[1,2], however, ERCP in patients with surgically altered gastrointestinal anatomy (SAGA) is far more challenging because of the inability of the endoscope to reach the blind end due to the long bowel passage, and of the complicated angulation. Some acute angled surgical limbs preclude the scope maneuverability and hinder the scope advancement.

The success of ERCP in patients with SAGA is affected by methods of surgical operations[3], and it often fails despite all the efforts. Consequently, many patients with SAGA are indicated for surgical or percutaneous operations, which is more invasive with greater risk of complications for patients than endoscopic therapy[4]. As an alternative procedure, percutaneous transhepatic cholangiography (PTC) is widely accepted, though is technically limited in such cases as; the absence of the dilated intrahepatic ducts, a contraindication due to the abdominal dropsy or compromised coagulation. In addition, PTC cannot establish an access to the pancreatic duct system[4]. Then surgery is left as the only alternative[5], though it brings about greater adverse events, longer hospital admission, and increased financial costs. Thus, the endoscopic interventional approaches have come to be preferred.

Since Katon *et al*[6] introduced the first endoscopic approach to Billroth-Ⅱ gastrectomy in 1975. In the late 1990s early 2000s, a number of papers studied on ERCP by using forward-viewing endoscopes or standard side-viewing duodenoscopes in various attempts, and the success rates widely ranged in 50%-92%[7-12]. As for Roux-en-Y reconstruction, Gostout *et al*[13] first reported the endoscopic approach in 1988. Since then, many attempts had been made by using duodenoscopes, pediatric colonoscopes, and oblique-viewing endoscopes, though the success rate was 33%-67% which was not satisfactory[12,14-16]. However, the advent of recently developed balloon assisted endoscopy (BAE) and spiral endoscopy (SE) radically gained the efficacy of endoscopic interventions in post-operative patients with not only Billroth-Ⅱ gastrectomy but also with Roux-en-Y reconstruction.

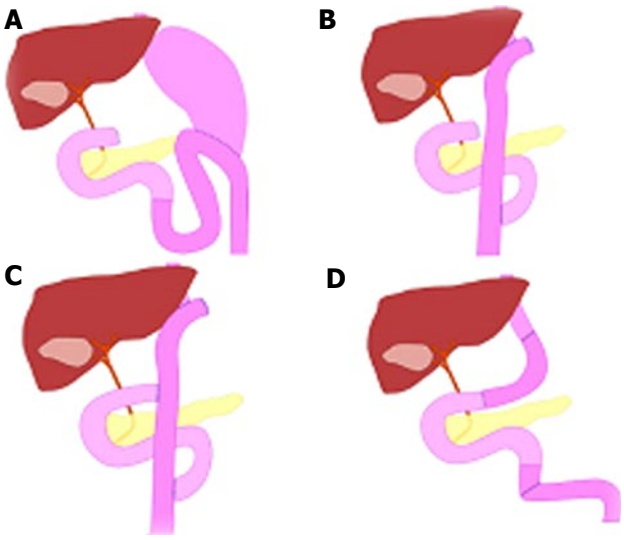

Figure 1 Schema of types of surgical anatomic reconstruction from gastrectomy. A: Billroth Ⅱ reconstruction; B: Roux-en-Y reconstruction; C: Double-tract reconstruction; D: Jejunal pouch interposition.

SURGICALLY ALTERED ANATOMY

In Japan, pancreaticoduodenectomy for treatment of pancreatic carcinoma and a total or partial gastrectomy for treatment of gastric diseases are often encountered. There are four common types of surgical anatomic reconstruction from gastrectomy; Billroth-Ⅱ reconstruction, Roux-en-Y reconstruction, double-tract reconstruction and jejunal pouch interposition (Figure 1). The number of Billroth-Ⅱ reconstruction has decreased due to the effective treatment of peptic ulcer disease whereas that of Roux-en-Y reconstruction has increased due to the recent spread of laparoscopic surgery. There are three common types of surgical anatomic reconstruction from pancreaticoduodenectomy; the Whipple Method, the (modified) Child surgery, the Cattell Method, and the Imanaga Method (Figure 2). Currently in Japan, the modified Child surgery is the first line reconstruction method for pancreaticoduodenectomies.

In United States in contrast, Roux-enY gastric bypass (RYGB) for morbid obesity[17-20], hepaticojejunostomy for living donor liver transplantation (LDLT)[21,22] or treatment of biliary injury or disease[23,24], and pancreaticoduodenectomy for ampulla neoplasia and pancreatic carcinoma[25,26] are more frequently encountered types of surgically altered anatomies. Because the severe morbid obesity is rarely encountered in Japan, RYGB for obese is not common and neither is hepaticojejunostomy for LDLT.

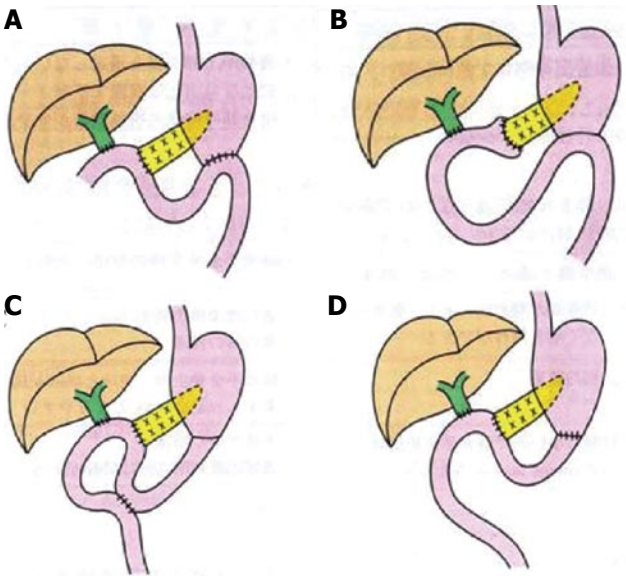

Figure 2 Schema of types of surgical anatomic reconstruction from pancreaticoduodenectomy. A: The Whipple Method; B: The (modified) Child surgery; C: The Cattell Method; D: The Imanaga Method.

Figure 3 Double-balloon endoscopy. The short type double balloon enteroscope (EC- 530B; FUJIFILM, Osaka, Japan) with a working channel of 2.8 mm diameter and a working length of 152 cm.

ENDOSCOPES

The invention of deep endoscopy has revolutionized the management of patients with mid-small-bowel diseases. Since the first introduction of double-balloon endoscopy (DBE) by Yamamoto[27] in 2001 (Figure 3), two additional techniques have become available, single-balloon endoscopy (SBE)[28,29] (Figure 4) and spiral endoscopy (SE)[30,31] (Figure 5). DBE and SBE entail a similar mechanism of advancement consisting of sequential bowel pleating by a push-pull technique that uses a balloon-fitted overtube with or without a second balloon inserted over the tip of a dedicated endoscope. The maneuver of the balloon or balloons in combination helps to hold and fix the intestine allowing the deep insertion by shortening the intestine. The inserting method of DBE (Figure 6) and SBE (Figure 7) is as shown in schemas. This technique enables the scope advancement selectively or retrogradely to reach the blind end in altered gastrointestinal anatomy with a high success rate. In contrast, SE is based on a different concept of insertion that pleats small bowel onto the endoscope to advance it through the lumen useing a rotating overtube [Discovery SB overtube (DSB); Spirus Medical, Inc., Stoughton, MA, United States]. This technique uses a spiral or raised helix-fitted overtube coupled with the endoscope, advanced as a unit into the small bowel by continuous rotation of the overtube in a manner similar to use of a corkscrew. An inner sleeve allows the independent motion of the overtube from the endoscope during advancement and withdrawal. The main difference between BAE and SE is that the latter uses a more or less continuous pleating of the small bowel by a clockwise rotation of the overtube rather than the push-pull technique. Unfortunately, SE is not currently commercially available.

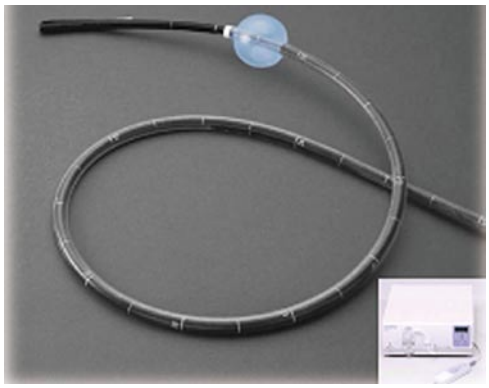

Figure 4 Single-balloon endoscopy. The standard type double balloon enteroscope (SIF- Q260; Olympus Systems, Tokyo, Japan) with a working channel of 2.8 mm diameter and a working length of 200 cm.

Figure 5 Spiral endoscopy. Discovery SB overtube over the snteroscope.

Characteristic of DBE

There are two types of DBE. One is with a 2.2 mm working channel for observations, introduced in 2003. The DBE, EN-450P (FUJIFILM, Osaka, Japan) and the other is for treatments with a 2.8 mm working channel. For the treatment-type scope, it can be sorted into two types. The first type was introduced in 2004, the standard type DBE, EN-450T5 (FUJIFILM, Osaka, Japan) with a 2.8 mm working channel and a 200 cm working length. The second type is the short type DBE, EC-450BI5 (FUJIFILM, Osaka, Japan) with a 2.8

Table 1 Information of balloon assisted endoscopy in Japan

	FUJIFILM					OLYMPUS		
	EN-450P/20	EN-450T5	EN-580T	EC-450BI5	EI-530B	SIF-Q260	SIF-Y 0004 (the first generation)	SIF-Y 0004 (the second generation)
	Standard type	Standard type	Standard type	Short type	Short type	Standard type	Short type	Short type
Release date (yr)	2003	2004	2013	2005	2011	2007	Prototype	Prototype
Direction of view	Forward view	Forward view	Forward view	Forward view	Forward view	Forward view	Forward view	Forward view
Angle of view	120°	140°	140°	140°	140°	140°	120°	120°
Outer diameter (mm)	8.5	9.4	9.4	9.4	9.4	9.2	9.2	9.2
Total length (mm)	2300	2300	2300	1820	1820	2305	1840	1840
Working length (mm)	2000	2000	2000	1520	1520	2000	1520	1520
Working channel (mm)	2.2	2.8	3.2	2.8	2.8	2.8	3.2	3.2
Passive bending part	No	No	No	No	No	No	No	Yes

mm working channel and a 152 cm working length that was introduced in 2005 as a colonoscope, and subsequently in 2011 another short type DBE EI-530B (FUJIFILM, Osaka, Japan) was introduced with a 2.8 mm working channel and a 152 cm working length as a pancreatobiliary scope. The short type DBE with the 152 cm working length is preferred and used rather than the standard type DBE with the 200 cm working length to perform ERCP in patients with (SAGA), because the 152 cm working length of the short type DBE allows the availability of almost all the ERCP-related devices, whereas the 200 cm working length limits the use of those devices.

In 2013, the treatment-type scope (EN-580T; FUJIFILM, Osaka, Japan) with a 3.2 mm working channel was introduced after further improvement, though it remained as the standard type with a 200 cm working length. For the use in ERCP in patients with SAGA, further development of short type DBE is strongly expected.

Characteristic of SBE

In 2007, Olympus introduced the standard type SBE (SIF-Q260; Olympus Medical Systems, Tokyo, Japan) with a 2.8 mm working channel and a 200 cm working length. Currently in Japan, only the standard type SBE is commercially available. Though, the short type SBE with a 3.2 mm working channel and a 152 cm working length (SIF-Y0004; Olympus Medical Systems, Tokyo, Japan), has been newly developed as the first-generation prototype. Some papers have been already written about the use of this scope for ERCP reporting that the 3.2 mm-working channel of the short type SBE allowed a smooth pushing-in and pulling-out action of devices, facilitating the employment of devices including a covered metallic stent that had been not applicable with the 2.8 mm working channel, which consequently enabled almost all the treatments that were equivalent to those of the conventional ERCP[32-35]. Additionally, the short type SBE (SIF-Y0004; Olympus Medical Systems, Tokyo, Japan) has been recently introduced as the second-generation prototype. This new endoscope is equipped with a passive bending part. This device helps the scope to pass and advance smoothly in the small intestine, which makes a special feature of this scope, as well as the 3.2 mm working channel that facilitated almost all the treatments equivalent to those of conventional ERCP. Some papers have been already written about ERCP using this scope[34,35], implying that deep insertion to the blind end using the second-generation prototype was easier than that using the first-generation prototype. With the equipment of this new device, the excelling performance in deep insertion to the blind end seems to be highly expected. Characteristics of BAE are summarized in Table 1.

ENTERING THE AFFERENT LIMB BY TYPE OF SURGICAL RECONSTRUCTION

The method of insertion to the blind end differs according to the type of surgical reconstruction. A full comprehension of every feature of respective reconstruction method is essential.

Billroth Ⅱ gastrectomy

In a case with Billroth Ⅱ gastrectomy, there are short afferent loop (SAL) and long afferent loop (LAL). The latter contains a jejunojejunostomy called the Braun anastomosis between the afferent and the efferent limbs. As for SAL, the angulation of gastrojejunostomy is acute, and it is difficult to identify the intestinal orifice that is possibly-be-the afferent limb, as well as to insert. The afferent limbs often appear in the upper left direction over the normal anastomosis in the monitor with its lumen closed. Generally, identification of the afferent limb is challenging due to the complicated angulation of gastrojejunostomy, however once the scope is inserted, the blind end can be reached using conventional scopes such as duodenoscopes or forward-viewing endoscopes in a short time owing to the short length of afferent limb. Ciçek *et al*[36] reported that the success rate of reaching the blind end in patients with simple Billroth Ⅱ gastroenterostomies using the duodenoscope was 83%.

In LAL, identification of the afferent limb is easy and the angulation is obtuse, which facilitates the scope insertion to the afferent limb because two intestinal orifices should be visible from the gastric lumen and either can be inserted easily. However due to the

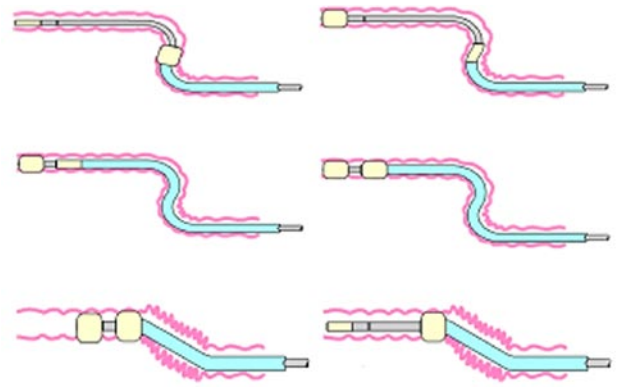

Figure 6 Schema of double-balloon endoscopy insertion.

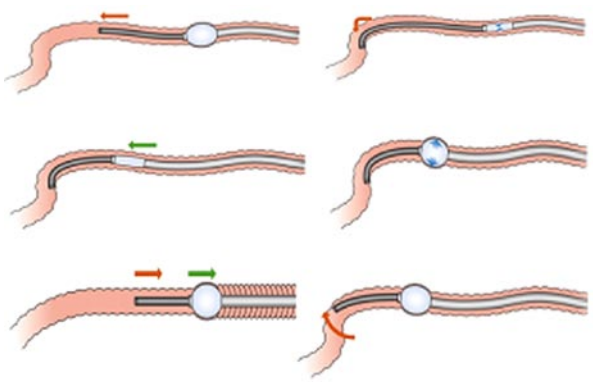

Figure 7 Schema of single-balloon endoscopy insertion.

longer length of the afferent limb it requires a longer duration to reach the blind end. It also precludes the advancement to the blind end. Thus, deep insertion using the conventional scopes is quite difficult.

In patients with both a Billroth Ⅱ gastroenterostomy and an additional Braun anastomosis, Çiçek *et al*[36] reported that the success rate was lowered to 29% for reaching the blind end. Whereas, Wu *et al*[37] reported the success rate of reaching the blind end in patients with both a Billroth Ⅱ gastroenterostomy and an additional Braun anastomosis was 90% even by using duodenoscopes by inserting the middle entrance of the lumen. Lin *et al*[38] reported the success rate of reaching the blind end using a duodenoscope was 69%. Furthermore in all the unsuccessful cases DBE was employed for the reattempted session and could successfully access the blind end. Also, in our previous report using short type DBE, the success rate of reaching the blind end was 100%[39]. In cases with Braun anastomosis, we would also attempt the insertion to the middle entrance as Wu *et al*[37] reported. The Braun anastomosis shows like a maze. It is often considered as a disadvantage for endoscopic insertion, however when the efferent limb was entered by error, the scope can always return from the Braun anastomosis to the efferent limb. Applying the technique to insert the middle entrance, the Braun anastomosis is not necessarily a disadvantage for the scope insertion, rather can be an advantage.

Roux-en-Y reconstruction

In a case with Roux-en-Y reconstruction, identification of the afferent limb in Y anastomosis is very difficult. Also, the insertion is possibly hindered by the acute angulation of the afferent limb and the severe adhesion as a consequence of the long intestine to the blind end. In comparison with the cases of Billroth Ⅱ gastrectomy, entering the afferent limb in cases with Roux-en-Y reconstruction is considered much more difficult. There are three challenges to be overcome for a successful insertion in cases with Roux-en-Y reconstruction.

The first challenge is identification of the afferent limb. It is difficult to identify the afferent limb in jejunojejunal anastomoses. Because of the maze-like feature of that area, endoscopists often lose their way or misjudge the orientation. Recently, Yano *et al*[40] reported a method using an intraluminal injection of indigo carmine to identify the afferent limb. The success rate was 80%, which suggests it should be helpful in identification of the afferent limb. However, the success rate based on our experience was approximately 50%. (unpublished observations) The divergence of the results could be reasoned that Yano *et al*[40] performed the procedure with the patient in a left-lateral position, whereas we performed in a pronation. Different postures in patients could have caused the divergence between the results.

The second challenge is the management of the complicated angulation in jejunojejunal anastomosis and the length of the afferent limb. It requires endoscopist's experience and skill to control the of sharp angulation of jejunojejunal anastomosis in order to reach the afferent limb, which in some patients forms an angle of up to 180 degrees. Shah *et al*[41] reported the success rate of deep insertion could be raised by change of patient's position from the typical semi-prone to a left-lateral or supine position during the procedure. Roux-en-Y gastric bypass (RYGB) is a particularly challenging postsurgical anatomy in terms of the length of the afferent limb. It consists of the long limb (often > 100 cm) that is traversed from the gastrojejunal orifice to the jejunojejunal anastomosis to reach the afferent small-bowel limb[14]. This reconstruction method is frequently performed in the United States for morbid obesity. Therefore, it was reported laparoscope-assisted ERCP was more efficient than endoscope-assisted ERCP for RYGB[42,43]. The RYGB is infrequently performed in Japan. We assume that the primary disease and application of surgery method differ to some extent in gastrointestinal anatomy between the United States and Japan.

Adhesions are the third challenge, which are frequently observed in patients with SAGA. In Japan, lymphadenectomy of malignant tumors is likely to be performed, which often results in post-surgical severe adhesion. They often preclude the scope advancement, and if scope insertion to this lesion is forced by power, it increases a risk of perforation and bleeding. Therefore

a careful maneuver and the discretion to withdraw are necessary for endoscopists.

In order to challenge these three obstacles, various attempts have been made and reported. Hintze *et al*[12] reported that the success rate of reaching the ampulla in Roux-en-Y anastomoses was 33%, compared with 92% in Billroth Ⅱ anatomy. Wright *et al*[14] reported a use of colonoscopy to access the biliary orifice and a guide wire for a duodenoscope to attempt ERCP in 15 patients with long-limb Roux-en-Y anastomoses. Kikuyama *et al*[16] used the oblique-viewing endoscope in couple with an overtube and reported a high success rate, though it was based on the small case series. Generally the results were not sufficiently practical or satisfactory.

Recently, two multicenter studies have been reported on the use of overtube-assisted endoscopy in the United States. One multicenter study[41] observed 129 patients (180 procedures) focusing only on Roux-en-Y reconstruction, and reported that the success rate of reaching the papilla or the hepaticojejunostomy site was 71% using several scopes such as DBE, SBE and SE. They concluded there was no divergence in the result caused by the type of applied scopes, however, in the 3/4 of unsuccessful cases where endoscopy-ERCPs failed were simply due to the failure of reaching the blind end, which suggested that the success of endooscopy-ERCPs were significantly affected by the result of the deep insertion to the blind end. It indicates that insertion to the blind end is quite challenging and prerequisite for performing ERCP in cases with Roux-en-Y reconstruction. The other multicenter study[44] focused on ERCP in 79 patients using the short-type DBE for several anatomical variations. The success rate of reaching the blind end was 90% (based on success rates of 82% for Roux-en-Y gastric bypass, 95% for pancreatoduodenectomy, and 100% for Billroth Ⅱ gastrectomy, hepaticojejunostomy, Roux-en-Y hepaticojejunostomy, Roux-en-Y gastrojejunostomy, choledochojejunostomy, and Roux-en-Y pancreaticojejunostomy). They reported a very high success rate of 90% to reach the papilla or the hepaticojejunostomy site applying only the short type DBE. They raised two points as reasons for their good result owing to several advantages regarding the short DBE, which is quite agreeable: (1) DBE might have better maneuverability than the long conventional DBE, which is especially useful in patients with post-surgical severe adhesions; and (2) DBE allowed endoscopists to apply a power pressure more effectively to the endoscope, which might have raised the success rate of reaching the papilla or anastomosis.

REACHING THE BLIND END WITH OVERTUBE-ASSISTED ENDOSCOPY

Reaching the blind end with BAE

SBE and DBE are based on the same concept of insertion. The difference is the presence or absence of the balloon at the tip of the endoscope. The absence of a balloon fitted to the tip of the endoscope impairs the stability in case with severe adhesions around the blind end. The slippery feature of intestine prevents the tip of the endoscope from being fixed still and orienting into the required direction to follow the overtube, which eventually hinders the deep advancement of overtube. Tsujikawa *et al*[28] suggested that the DBE was advantageous in cases with sharp angulations of the small intestine, because the balloon on the tip of the DBE could help pass around such angulations better than the hook-shaped tip of the SBE. In comparison with DBE, it is assumed that SBE is more disadvantageous in a performance of deep insertion. Shah *et al*[41] reported the success rates of reaching the blind end in patients with Roux-en-Y gastric bypass using standard type SBE (n = 22) or DBE (n = 15), using both the standard and the short type DBE, was 73% in the SBE group and 87% in the DBE group. It suggested that DBE showed a better performance in deep insertion to the blind end. However, the new short type SBE with the passive bending part has been introduced in order to improve the success rate of insertion to the blind end. Obana *et al*[33] reported the success rate of insertion to the blind end using the short type SBE without the passive bending part was 73%, which was relatively low. Recently we have reported the success rate using the short type SBE with the passive bending part was 92%[34]. We assume that the success rate of deep insertion to the blind end might have been raised by the use of short type SBE equipped with the passive bending part. Today several challenges are yet to be overcome for deep insertions using BAEs into the blind end.

Reaching the blind end with SE

SE is based on the totally different concept of insertion from that of BAE. Previous small studies have suggested that SE allow more efficient advancement into the small bowel than BAE, however, there are not much paper written regarding the insertion to the blind end in patients with (SAGA) using SE. Therefore, sufficient data are not available to evaluate the SE in point of success rate of deep insertion, complication morbidity and efficacy. To evaluate the efficacy and the safety of this method, more studies and assessment in a larger number of cases are necessary.

OVERTUBE-ASSISTED ERCP

Many studies of DBE-assisted ERCP have been made since 2007[39,41,44-61]. And studies of SBE-assisted ERCP were subsequently introduced in 2009[62-69], followed by the studies of SE-assisted ERCP in 2011[70-72]. As the DBE was introduced prior to the development of the SBE and SE, there existed more number of reports of successful ERCP using DBE in patients with PD than that of the SBE and SE. In comparison of the results before and after the advent of BAE and/or SE, it is obvious that

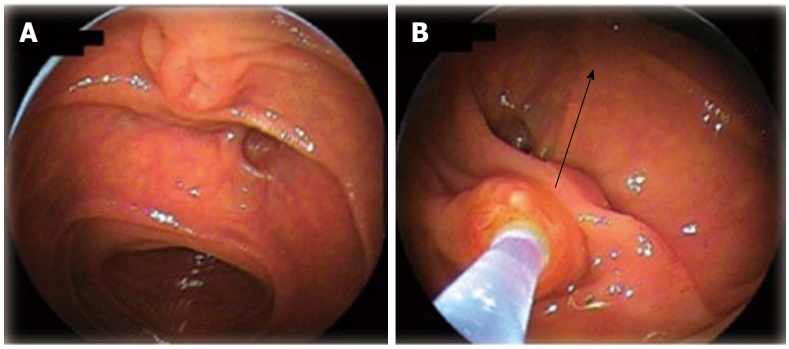

Figure 8 Biliary cannulation using double-balloon endoscopy in a patient with papilla. A: Papilla when the blind end was accessed; B: Locating papilla in 6 o'clock direction in the monitor, and performing cannulation adjusting the axis of catheter into 12 o'clock direction along the biliary duct.

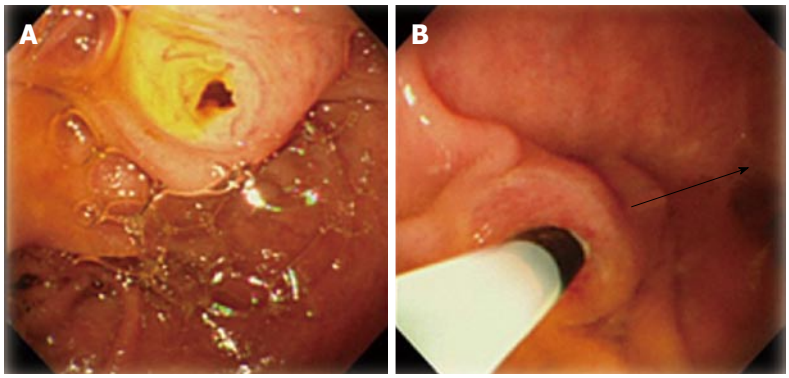

Figure 9 Biliary cannulation using single-balloon endoscopy in a patient with papilla. A: Papilla when the blind end was accessed; B: Locating papilla in 8-9 o'clock direction in the monitor, and performing cannulation adjusting the axis of catheter into 3 o'clock direction along the biliary duct.

the success rate has radically improved to a satisfactory level.

DBE-assisted ERCP

There are a lot of studies on DBE-assisted ERCP with wide ranging results. The success rate of ERCP-related interventions varied 60%-100%[39,41,44-61], which was probably because many studies were based on a small number of cases. We have reported a large case single center study[39], as a single center study in which we evaluated 103 procedures DBE-assisted ERCP by type of reconstruction method in 68 patients. The overall success rate for ERCP was 95% (based on success rates for Roux-en-Y reconstruction, Billroth Ⅱ reconstruction, and pancreatoduodenectomy of 91%, 100%, and 100%, respectively). In all successful ERCP cases, endoscopic therapeutic interventions were successfully accomplished. One multicenter study[41] reported the overall ERCP success rate was 63%. The success rate of ERCP using SBE and DBE was similar between Roux-en-Y gastric bypass and other long-limb surgical bypass. It also reported that the success rate of ERCP in cases where the blind end was successfully reached was 88%, which was satisfactory though they explained the success rate was lowered because many cases had contained papilla. Itoi *et al*[63] reported the success rate of ERCP using the standard type SBE was 72.3% mentioning that the biliary approach in patients with naïve papilla was difficult[63]. It is agreeable, however, in our previous study[39], the success rate of cannulation into papilla was 97%, suggesting the different type of applied scopes could affect the divergence of the results. For instance, because the position of the working channel of DBE is located at 6:30, an attempt to bring the papilla in a 6 o'clock direction in monitor will allow a down-angled maneuver that helps to fix the papilla still by a direct power pressure, which facilitates a stable cannulation (Figure 8). Whereas, the position of the working channel of SBE is located at 9 o'clock, which makes difficult to fix the papilla, precluding a stable cannulation as a consequence (Figure 9). Whereas Shah *et al*[41] concluded the type of scopes did not affect their result, though they used mostly the standard type DBE and SBE with the 200 cm working length in many cases. Namely, it could be inferred that not only using the DBE but the short type was the best appropriate scope for cannulation in cases with papilla. Siddiqui *et al*[44] reported the overall ERCP success rate using only the short-type DBE was 90% raising a reason for the excellent result as; the short DBE allowed the use of commercially available ERCP cannulas for performance of wire-guided cannulation, and therapeutic instruments could be applied to carry out successful therapeutic treatments.

SBE-assisted ERCP

Dellon *et al*[64] evaluated a use of the standard type SBE for diagnostic and therapeutic ERCP. They observed 4 patients with Roux-en-Y anatomy in total. (1 patient with RYGB, 2 patients with Roux-en-Y anatomy caused by bile duct injury, and 1 patient with Roux-en-Y anatomy after liver transplantation). The overall success rate of the therapeutic ERCP on the first session was 50%. In this report, the standard type SBE with 200 cm working length that was only applicable to limited variety of devices was used for the therapeutic ERCP,

Table 2 Review studys evaluating endoscopic retrograde cholangiopancreatography using several enteroscopy in patients with altered gastrointestinal anatomy

Ref.	No. of cases	Type of scope	Enteroscopy success (%)	Success rate of ERCP	Overall ERCP success (%)
Mehdizadeh *et al*[48]	5	Standard type DBE	67	100	67
Mönkemüller *et al*[53]	18	Standard type DBE	94	85	83
Maaser *et al*[4]	11	Standard type DBE	100	64	64
Kuga *et al*[59]	6	Standard type DBE	100	83	83
Tsujino *et al*[49]	12	Short type DBE	100	94	94
Siddiqui *et al*[44]	79	Short type DBE	89	90	81
Shimatani *et al*[39]	103	Short type DBE	97	96	94
Tomizawa *et al*[69]	22	Standard type SBE	68	73	50
Itoi *et al*[63]	13	Standard type SBE	92	83	77
Dellon *et al*[64]	4	Standard type SBE	75	67	50
Yamauchi *et al*[32]	31	Short type SBE	90	89	81
Obana *et al*[33]	19	Short type SBE	79	66	53
Shimatani *et al*[34]	26	Short type SBE	92	92	85
Lennon *et al*[70]	29	Standard type SBE	55	87	48
Shah *et al*[41]	27	Standard type DBE	85	85	63

ERCP: Endoscopic retrograde cholangiopancreatography; DBE: Double balloon endoscopy; SBE: Single-balloon endoscopy.

which could have caused the unsatisfactory success rate of SBE-assisted ERCP.

However, along the recent development of the short type SBE, several reports have been made on the short type SBE-assisted ERCP. The overall success rate of ERCP was 78%-90%, which was higher than that of ERCP using the standard type SBE. It could be reasoned that the 152 cm working length allowed the use of more variety of available devices.

SE-assisted ERCP

Although only published in abstract form, some studies on SE-assisted ERCP have been made. In a multi-center study, Shah *et al*[41] reported 129 patients with surgically altered anatomy who underwent ERCP using SBE (*n* = 15), DBE (*n* = 22), and SE (*n* = 13). The ERCP success rates of each method were 60%, 63%, and 65%, respectively. Lennon *et al*[70] discussed the comparison of SE and SBE. They concluded there was no significant difference between SE and SBE, and their overall ERCP success rate was 44%.

A review of studies evaluating overtube assisted ERCP in patients with (SAGA) *via* various techniques is summarized in Table 2.

COMPLICATIONS

It is assumed that the morbidity of complications is affected by type of applied endoscopes and by method of surgical reconstruction. The common complications for overtube-assisted ERCP are comparable with those of conventional ERCP such as bleeding, perforation, and post-ERCP pancreatitis. There are few studies made only in a small case series, however, the actual rates of perforation, bleeding, and pancreatitis associated with overtuve-assisted ERCP is unknown.

Performing ERCP in Patients with SAGAposes a greater risk of complications than in patients with NGA[73,74]. The risk of retroperitoneal perforation in patients with Billroth II surgery has been reported as high as 7%-10%[74]. Regarding Roux-en-Y reconstruction, our previous study retrospectively observed 55 procedures, reporting that procedural complications developed in 5 of 55 procedures (9%)[39]. Shah *et al*[41] retrospectively observed 129 patients, reporting that procedural complications were observed in 16 of 129 patients (12%), including pancreatitis (mild = 4, severe = 1), mild bleeding (*n* = 1), abdominal pain requiring hospital admission (*n* = 3), and throat pain requiring physician contact (*n* = 4). Two perforations were also observed and 1 case of death occurred. However, apart from those, studies based on only small case series can be found[75,76]. In order to evaluate the safety and efficacy of the procedure, it is necessary to analyze and evaluate data of complications out of large case studies from multiple centers prospectively, particularly for Roux-en-Y reconstruction.

CONCLUSION

The endoscopic approach to PD in patients with (SAGA) has radically become practical. Development of new modalities such as DBE, SBE, and SE is in progress as a consequence of an increased demand for the endoscopic interventions. For the safety and a higher success of the procedures, further development of the scopes and devices, standardization of technical maneuverability, establishment of guidelines in decision making of indicated and contraindicated cases, and assessment of complications from a larger multi-center study are necessary.

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REVIEW

Endoscopic ultrasound guided interventional procedures

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Abstract

Endoscopic ultrasound (EUS) has emerged as an important diagnostic and therapeutic modality in the field of gastrointestinal endoscopy. EUS provides access to many organs and lesions which are in proximity to the gastrointestinal tract and thus giving an opportunity to target them for therapeutic and diagnostic purposes. This modality also provides a real time opportunity to target the required area while avoiding adjacent vascular and other structures. Therapeutic EUS has found role in management of pancreatic fluid collections, biliary and pancreatic duct drainage in cases of failed endoscopic retrograde cholangiopancreatography, drainage of gallbladder, celiac plexus neurolysis/blockage, drainage of mediastinal and intra-abdominal abscesses and collections and in targeted cancer chemotherapy and radiotherapy. Infact, therapeutic EUS has emerged as the therapy of choice for management of pancreatic pseudocysts and recent innovations like fully covered removable metallic stents have improved results in patients with organised necrosis. Similarly, EUS guided drainage of biliary tract and pancreatic duct helps drainage of these systems in patients with failed cannulation, inaccessible papilla as with duodenal/gastric obstruction or surgically altered anatomy. EUS guided gall bladder drainage is a useful emergent procedure in patients with acute cholecystitis who are not fit for surgery. EUS guided celiac plexus neurolysis and blockage is more effective and less morbid vis-à-vis the percutaneous technique. The field of interventional EUS is rapidly advancing and many more interventions are being continuously added. This review focuses on the current status of evidence vis-à-vis the established indications of therapeutic EUS.

Key words: Endosonography; Pancreatic pseudocyst; Celiac plexus; Choledochostomy; Cholecystostomy; Photochemotherapy; Abdominal abscess; Common bile duct; Pancreatic duct; Endoscopic ultrasound-guided fine needle aspiration

Core tip: Therapeutic endoscopic ultrasound (EUS) has found role in management of pancreatic fluid collections, biliary and pancreatic duct drainage in cases of failed endoscopic retrograde cholangiopancreatography, drainage of gallbladder, celiac plexus neurolysis/blockage, drainage of mediastinal and intra-abdominal abscesses and collections and in targeted cancer chemotherapy

and radiotherapy. The field of interventional EUS is rapidly advancing and many more interventions are being continuously added. This review focuses on the current status of evidence vis-à-vis the established indications of therapeutic EUS.

Sharma V, Rana SS, Bhasin DK. Endoscopic ultrasound guided interventional procedures. *World J Gastrointest Endosc* 2015; 7(6): 628-642 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i6/628.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i6.628

Endoscopic ultrasound (EUS) is an important diagnostic and therapeutic technique in the field of gastroenterology. The ability to visualise and access organs in vicinity of the gastrointestinal tract has opened this exciting field with many interventional EUS procedures now overtaking conventional approaches for treatment of various gastrointestinal diseases. While advances have been made in all aspects of diagnostic and therapeutic EUS, the present review will focus on advances in therapeutic EUS and use of EUS in drainage of pancreatic collections, celiac plexus neurolysis, biliary/pancreatic duct drainage, and in the drainage of intra-abdominal abscesses.

EUS GUIDED DRAINAGE OF PANCREATIC FLUID COLLECTIONS

Pancreatic fluid collections

Acute and chronic pancreatitis can be complicated by collections of varying nature composed of pancreatic juice and varying amounts of necrotic debris in patients with acute necrotising pancreatitis[1]. The morphological characteristics of pancreatic collections complicating acute pancreatitis seem to change with time and the amount of solid necrotic debris lessens with time[2]. Pancreatic fluid collections need to be drained if they get infected or become symptomatic and cause abdominal pain, gastric outlet obstruction or biliary obstruction. Radiological, surgical and endoscopic approaches have been used to drain pancreatic collections[3,4]. Broadly, collections needing drainage early in the course of illness when a wall has not yet formed are drained *via* percutaneous interventions while endoscopic drainage is feasible late in the course when wall has formed[5]. The distinction between the types of collection is important before drainage as the nature and outcome of drainage depend to a large part on the amount of solid debris present in the pancreatic fluid collections (PFCs)[6-8]. While non-necrotic collections have an excellent outcome with endoscopic drainage, the fate of necrotic collections is not as good. In one report while treatment success was 93.5% in pseudocyst drainage it was much lower at 63.2% for drainage of walled off necrosis[9]. Morphologic features like size and amount of debris predict the number of procedures needed as increasing size and amount of debris predict more number of procedures[8].

Endoscopic drainage vs EUS-guided drainage

While many centres continue to perform pancreatic pseudocyst drainage endoscopically, there is some evidence to suggest that EUS-guided drainage may be preferable. Two randomised trials have indicated a higher technical success especially in non-bulging lesions (Table 1)[10,11]. EUS-guided drainage is preferable in certain other clinical scenarios like presence of portal hypertension, collaterals around the collection, and presence of calcification in the wall[14,15]. A meta-analysis of available studies suggest that the technical success rates are higher for EUS guided drainage but the short term and long term results appeared to be similar[12]. In one of the report comparing the endoscopic and EUS guided drainage, median hospital stay was reported as similar with the two modalities[11]. Both reports indicate that the procedure time was not significantly different with either of the modality[10,11].

EUS guided drainage of PFCs

The drainage using EUS is done by using a linear echoendoscope which is advanced into the stomach or duodenum. The window is assessed using colour Doppler for any regional vascularity as well as the distance between the gastrointestinal tract wall and the cyst is measured. A 19 gauge EUS fine needle aspiration (FNA) is utilised to access the collection and contents aspirated for visual assessment as well as for analysis (cultures, amylase and carcinoembryonic antigen levels). Following this a guidewire is coiled into the cyst cavity and the tract is dilated[6,7,16]. Following this various modifications are available for the drainage of PFCs including single or multiple stentings, multistep procedure with initial nasocystic drain followed by placement of stent or insertion of fully covered self-expanding metallic stents[17]. Also, after resolution of PFC, removal of transmural stents may result in recurrence of PFCs[18]. Long term indwelling plastic stents, especially in patients with disconnected duct, is a preferred approach currently in these patients[19]. Multiple authors have reported good results of EUS guided drainage and Table 2 shows important studies reporting outcomes with EUS-guided drainage of PFCs[20-36].

Innovations

Use of metallic stents: Use of self expanding metallic stents (SEMS) has recently been advocated as they may provide a better drainage because of wider diameter and thus a quicker resolution of the symptoms[37]. Various removable stents with anti-migration features have been introduced for drainage of PFCs. Fully covered stents with dumbbell like shape have been introduced which provide lumen apposition and have lesser chances of migration[38]. Various innovations like insertion of plastic pigtail stents to prevent migration

Table 1 Comparison between endoscopic *vs* endoscopic ultrasound-guided drainage of pancreatic pseudocysts

Ref.	Patients and methods	Results
Park *et al*[10]	Randomised trial of conventional *vs* EUS guided drainage of pancreatic pseudocysts (n = 60)	EUS guided drainage has higher technical success (94% *vs* 72%). EUS preferable in non-bulging collections. Complications and pseudocyst resolution similar
Varadarajulu *et al*[11]	RCT of conventional *vs* EUS guided drainage (n = 15 each)	Higher technical success in EUS guided procedure (100% *vs* 33%) with lesser complications
Kahaleh *et al*[12]	Conventional drainage in bulging pseudocysts and absence of portal hypertension *vs* EUS guided in rest (n = 99)	No differences in short term or long term success and similar complications
Barthet *et al*[13]	Algorithm based approach of transpapillary (for small), EUS guided (nonbulging) or Conventional drainage of pseudocysts	EUS guided approach needed for atleast half of the patients

EUS: Endoscopic ultrasound; RCT: Randomized controlled trials.

Table 2 Endoscopic ultrasound guided drainage of pancreatic fluid collections (excluding self expanding metallic stents)

Ref.	Number	Outcome
Giovannini *et al*[20]	35 patients: 15 pseudocyst and 20 WON	Technical success: 94.3% Clinical success: 88.5%
Hookey *et al*[21]	116 patients (51 EUS guided transmural drainage)	Technical success: 93.8% Clinical success: 90.6%
Krüger *et al*[22]	35 patients (both pseudocysts and abscess)	Technical success: 94% Clinical success: 88%
Antillon *et al*[23]	33 patients: all pseudocysts	Technical success: 94% Clinical success: 90%
Lopes *et al*[24]	62 procedures: 36 pseudocysts and 26 abscesses	Technical success: 94% Clinical success: 84.3%
Ardengh *et al*[25]	77 patients with sterile PFCs	Technical success: 94% Clinical success: 91%
Varadarajulu *et al*[26]	60 patients: 36 pseudocyst and 24 with abscess/WON	Technical success: 95% Clinical success: 93%
Ahn *et al*[27]	47 patients with pseudocyst	Technical success: 89% Clinical success: 100%
Will *et al*[28]	132 patients: 31 pseudocysts (n = 32), 115 abscesses/WON	Technical success: 97% Clinical success: 96%
Seewald *et al*[29]	70 patients: including pseudocyst, WON, abscess	Technical success: 97.5% Clinical success: 83%
Puri *et al*[30]	40 patients with pseudocyst	Technical success: 100% Clinical success: 97%
Kato *et al*[31]	67 patients with pseudocyst	Technical success: 88% Clinical success: 83%
Künzli *et al*[32]	108 patients	Technical success: 97% Clinical success: 84%
Siddique *et al*[33]	87 patients with WON	Technical success: 99% Clinical success: 73.5%
Hocke *et al*[34]	30 patients with WON	Technical success: 96.7% Clinical success: 83.4%
Jürgensen *et al*[35]	35 patients with WON	Technical success: 100% Clinical success: 97%
Yasuda *et al*[36]	57 patients with WON	Technical success: 100% Clinical success: 75%

WON: Walled off necrosis; EUS: Endoscopic ultrasound; PFCs: Pancreatic fluid collections.

have been employed with these stents[39]. The major benefit of SEMS is likely to be in walled off necrosis (WON) as they may provide ease of repeated access for necrosectomy, however this remains to be proven in prospective studies. Table 3 depicts the studies where metallic stents were used in management of PFCs.

Non-fluoroscopic drainage: It has been demonstrated that EUS-guided drainage is feasible even without fluoroscopic control[6,48]. Seicean *et al*[48] have demonstrated the utility of EUS in drainage of PFCs in 24 patients and documented complete resolution in 83.3% cases. However difficulty arose in PFCs with thickened wall for which fluoroscopic control was recommended by the authors. We have also demonstrated the efficacy of EUS in draining non-bulging PFCs in 20 patients in absence of fluoroscopic control. Only one patient needed percutaneous intervention amongst these 20 patients[6]. In another report of EUS guided drainage of 22 patients with PFCs, drainage was technically feasible in 19 patients even in absence of fluoroscopy. Success after single procedure was noted in 59% patients[49].

Creation of multiple drainage routes: In management of walled off necrosis, creation of a single enteral opening may not provide adequate drainage of the collection. In this regard it may be better to have multiple access sites into the cavity which may help in improving drainage and irrigation of the cavity. Dual modality drainage involving percutaneous and endoscopic drainage simultaneously has been advocated for achieving this end[50]. A purely endoscopic procedure: EUS guided multi transluminal gateway technique has been evaluated and reported to have a high success (91.7%) vis-à-vis convention drainage (52.1) in a non-randomised study[51]. Prospective reports validating this approach are awaited.

Forward viewing echoendoscope: A multicentre randomised trial reported use of a forward viewing echoendoscope for drainage of PFCs. The technical success rates, mean procedure times, ease of access and complication rates were similar to the oblique-viewing echoendoscope indicating lack of any benefit with use of forward viewing echoendoscope for drainage of PFCs[52].

Table 3 Use of metallic stents for endoscopic ultrasound guided drainage of pancreatic fluid collections

Ref.	Population	Stent	Design	Outcome
SEMS				
Talreja *et al*[17]	18 patients with PFCs	FCSEMS (biliary stent)	Prospective cohort	95% success
Belle *et al*[40]	4 patients with WON	PCSEMS	Case series	100% clinical success
Fabbri *et al*[41]	22 patients with infected PFCs	FCSEMS (biliary)	Case series	77% clinical success
Penn *et al*[39]	20 with PFCs	FCSEMS (biliary) with plastic pigtail	Case series	Technical success 100%, clinical success 85%
Weilert *et al*[42]	18 patients with PFCs	FCSEMS	Case series	Clinical success in 78%
LACSEMS				
Shah *et al*[43]	Pseudocyst and WON (n = 33)	AXIOS (EUS guided in 30/33)	Prospective cohort	91% technical success, 93% resolution of PFC
Walter *et al*[44]	46 patients WON and 15 pseudocyst	AXIOS stent	Prospective cohort	Technical success: 98%, clinical success: 93% in pseudocyst and 81% in WON
Gornals *et al*[45]	9 patients with PFCs	AXIOS	Case series	Technical success in 88% and 100% clinical success
Itoi *et al*[46]	15 patients with pseudocysts	AXIOS	Retrospective case series	100% clinical success
Yamamoto *et al*[37]	9 PFCs, 5 pseudocyst and 4 WON	FCSEMS (Nagi stent)	Retrospective case series	77.8% clinical success
ESOPHAGEAL SEMS				
Sarkaria *et al*[47]	17 patients with WON	Esophageal FCSEMS	Retrospective case series	88% clinical success

SEMS: Self expanding metallic stents; PFCs: Pancreatic fluid collections; FCSEMS: Fully covered SEMS; WON: Walled off necrosis; LACSEMS: Lumen apposing covered SEMS.

Others

Access to the cavity may be difficult in patients with thick wall between the gastric/duodenal lumen and the cavity and therefore the tract may be difficult to dilate. To overcome this use of wire guided bent needle knife to obtain a wide access has been used[53]. A double guidewire technique utilising a double lumen catheter has been advocated to avoid the hassle of repeated need for cannulation of pseudocyst for placing multiple endoprosthesis[54]. A modification of the dual-lumen biliary brush catheter has also been used to place multiple guidewires into the cyst cavity and thereby allowing placement of multiple stents[55]. A novel exchange free access device has also been used for EUS guided drainage of PFCs and has an inner trocar for puncture and an outer dual balloon for dilatation of the tract reducing the need for multiple exchanges[56,57]. Numerous other innovations like use of hydrogen peroxide and streptokinase have been used but comparative data vis-à-vis control group is not yet available[58,59].

Drainage of PFCs is an important therapeutic application of EUS with excellent technical and clinical outcomes. We believe that merely dividing walled off PFCs into pseudocysts and WON may be too simplistic and it would be better to have three subgroups including acute postnecrotic pseudocyst (< 10% solid debris), walled off liquid necrosis (10%-40% solid content) and walled off solid necrosis (> 40% solid debris) as this has implications on management and success of endoscopic drainage[60]. We have previously shown that the amount of necrosis predicts the therapy needed in PFCs. Whilst those with < 10% debris need only one session of drainage, those with 10%-40% solid debris needed ≥ 2 sessions and the group with even higher (> 40%) debris needed direct endoscopic debridement or surgical necrosectomy[8]. Based on this, we follow an algorithmic approach (Figure 1) for management of PFCs at our institution.

EUS GUIDED BILIARY ACCESS

Endoscopic retrograde cholangio-pancreaticography (ERCP) is the standard approach to drain an obstructed biliary tract but may fail due to a number of factors like inaccessible papilla or a failure to cannulate it. In these situations, radiological or surgical drainage is needed. EUS guided biliary drainage is emerging as an alternative to a failed ERCP[16]. EUS guided approaches include transmural drainage (hepaticogastrostomy or choledochoduodenostomy), a rendezvous procedure or an antegrade approach[61]. EUS guided transluminal drainage (EUS-TLD) is achieved by bile duct puncture from the stomach or the duodenum using EUS-FNA needle. Occasionally choledochoantrostomy or hepaticoesophagostomy has also been described for achieving biliary drainage[62-64]. After obtaining a cholangiogram a guidewire is placed into the biliary system and the tract dilated followed by insertion of stent to achieve drainage of biliary system into the stomach or the duodenum. While duodenal station is used to achieve access into the common bile duct, gastric station allows access to the left lobe intrahepatic biliary radicals[61]. Access to right sided biliary system has also been described[65]. Table 4 depicts the major reports of EUS guided transluminal access to biliary

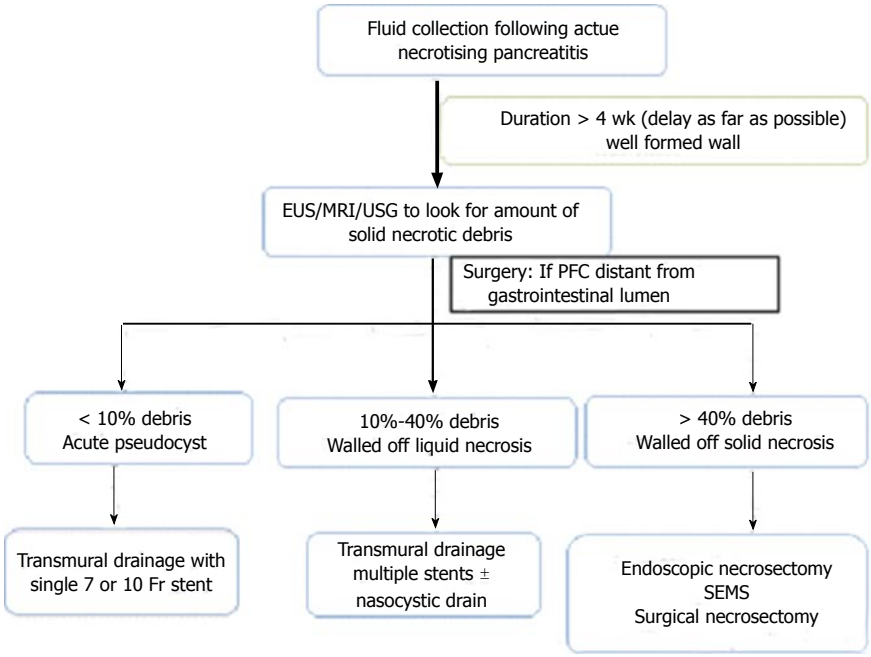

Figure 1 Proposed endoscopic treatment algorithm for walled off pancreatic necrosis. EUS: Endoscopic ultrasound; MRI: Magnetic resonance imaging; PFC: Pancreatic fluid collection; SEMS: Self expanding metallic stents.

Table 4 Endoscopic ultrasound guided transluminal biliary drainage

Ref.	Number	Etiology	Technical success	Clinical success	Complication rates
Takada *et al*[66]	26 17 CCD, 6 HG, 2 CCA, 1 HJ	Malignant	90.6%	100%	20.7%
Kawakubo *et al*[67]	64 CCD: 44 HG: 20	Malignant	95%	100%	19%
Prachayakul *et al*[68]	21 CCD: 6 HG: 15	Malignant	95.2%	90.2%	9.5%
Hara *et al*[69]	18 CCD	Malignant	94%	94%	11%
Song *et al*[70]	15 CCD	Malignant	86.7%	100%	23.1%
Kim *et al*[71]	13 CCD: 9 HG: 4	Malignant	92.3%	91.7%	30.7%
Park do *et al*[72]	57 CCD: 26 HG: 31	Both benign and malignant	96.5%	89%	20%
Komaki *et al*[73]	15 CCD	Malignant	93%	100%	26.7%
Hara *et al*[74]	18 CCD	Malignant	94%	100%	17%
Khashab *et al*[64]	20 HG: 3 CCD: 15 HE: 2	Malignant	95%	86.3%	10%
Vila *et al*[75]	60 HG: 34 CCD: 26	Both benign and malignant	64.7% and 86.3%	63.2%	15.1%
Attasaranya *et al*[76]	25 HG: 16 CCD: 9	Both benign and malignant	77%	96%	35%

CCD: Cholecystoduodenostomy; HG: Hepaticogastrostomy; CCA: Cholescystoantrostomy; HJ: Hepaticojejunostomy.

system. EUS guided rendezvous is achieved by creation of a temporary access to the biliary tree using EUS guided approach in patients with failed cannulation but with accessible papilla. The guidewire is then negotiated across the obstruction into the duodenum through the papilla and is then retrieved using snare and thereby providing a conduit for further ERCP[61]. This approach is, therefore, useful in failed ERCP but accessible papilla. The approach from the stomach and first part of duodenum is considered to be stable but the ampullary direction of guidewire is achieved best from the stomach and second part of duodenum[61]. Table 5 depicts the major reports of EUS guided rendezvous procedures and their outcomes. EUS guided antegrade approach is the use of temporary EUS guided access created from the duodenum or stomach for placement of stents or balloon dilatation without the scope reaching the papilla. The reported success rate for this procedure is 77% and the complication rate is 5%, however large studies are lacking[61].

EUS-TLD is associated with significant complications including perforation, bile leak, bleeding, and stent dysfunction or migration. The use of EUS-TLD has also been reported to be as efficacious as transpapillary drainage in patients with previous duodenal stents with a higher stent patency rate with EUS-TLD[84]. SEMS are preferred over plastic stents as they provide a larger diameter and therefore are likely to remain patent for longer periods and the risk of bile leaks is likely to be less with SEMS. SEMS also make a reinsertion of stent easier as stent can be placed into the previous SEMS[85]. Both EUS-TLD and placement of duodenal SEMS in patients with obstructive jaundice and duodenal obstru-

Table 5 Endoscopic ultrasound rendezvous procedures for biliary drainage

Ref.	Number	Technical success	Clinical success	Complications
Khashab *et al*[64]	13 (EH: 11, IH: 2)	100%	100%	15%
Tarantino *et al*[77]	4 (EH: 4)	50%	100%	13%
Dhir *et al*[78]	20	100%	100%	15%
Dhir *et al*[79]	17 TH, 18 EH	100% for EH and 94.1% for TH	100%	Higher for TH *vs* EH
Park do *et al*[80]	20 (14 IH and 6 EH)		80%	10%
Kawakubo *et al*[81]	14 (9 EH and 5 IH)	100%	100%	14%
Dhir *et al*[82]	58 (all EH)	-	98%	3.4%
Iwashita *et al*[83]	40 (31 EH and 9 IH)		73%	13%

EH: Extrahepatic; IH: intrahepatic.

ction due to unresectable periampullary lesions has been reported as a single step procedure with use of linear echo-endoscope[86].

EUS guided approaches have also been compared with percutaneous approach for biliary drainage. In a randomised study comparing percutaneous and EUS guided approaches in 25 patients with unresectable biliary obstruction, the technical success, clinical success, cost and complications were similar amongst both the groups suggesting that either could be used as an alternative for biliary drainage[87]. However a recent report comparing 51 patients who underwent percutaneous transhepatic biliary drainage (PTBD) with 22 patients who underwent EUS-TLD indicated that the technical success was higher for PTBD. The authors however recommended EUS-TLD as the initial procedure of choice as it needed lesser re-interventions reducing costs of therapy as also a lower adverse event rate[88]. In a similar report where 50 patients were retrospectively evaluated success of internal stenting as well as complication rates were more favourable in the EUS-TLD group. While internal stenting could be achieved in 92% patients in EUS-TLD group, it could be achieved only in 46% of PTBD group[89]. Amongst EUS guided approaches, transhepatic access seems to increase the risk of complications vis-à-vis transduodenal access of the biliary tree[78]. An approach has been suggested for the use of various EUS guided methods for achieving biliary drainage in different clinical settings. If ampulla is inaccessible, EUS-TLD is the initial choice. If papilla is accessible rendezvous should be attempted but if it is not possible to cross the lesion/stricture then EUS-TLD can be undertaken. Antegrade approach may be better suited for surgically altered anatomy where the procedure is needed for benign lesions[61].

EUS GUIDED GALL BLADDER DRAINAGE

The emergent gall bladder drainage is usually done radiologically but availability of EUS has made it possible to drain the gall bladder endoscopically. This may be indicated in situations like acute cholecystitis in patients who are unsuitable for surgery and have not improved with antibiotics[90]. In a systematic review of endoscopic drainage of gallbladder using nasogallbladder drainage in 194 patients and gallbladder stenting in 127 patients the technical success rates were 81% and 96%, clinical success rates were 75% and 88% and complication rates were 3.6% and 6.3%, respectively[90,91]. In a randomised study of patients with acute cholecystitis who were assigned to undergo either an EUS guided drainage or a percutaneous drainage of gall bladder the technical success rates were similar as were the complication rates suggesting that EUS guided approach is feasible for gall bladder drainage with outcomes comparable to the percutaneous approach[92]. Major reports (> 10 patients) on EUS guided drainage of gall bladder are shown in Table 6.

Table 6 Endoscopic ultrasound guided gall bladder drainage for acute cholecystitis

Ref.	Number	Technical success	Clinical success	Complications
Jang *et al*[92]	30	97%	100%	7%
Lee *et al*[93]	9	100%	100%	11%
Song *et al*[94]	8	100%	100%	37%
Jang *et al*[95]	15	100%	100%	13%
de la Serna-Higuera *et al*[96]	13	85%	85%	15%

Gall Bladder drainage can be achieved by use of either plastic or metallic stents or use of naso-gallbladder drains[94,95]. The complications may include bile leak, perforation and pneumo-peritoneum. In a report evaluating long term outcomes in 56 patients with acute cholecystitis who had underwent EUS guided gallbladder drainage the stent patency was 86% over 3 years. Four patients had late adverse events including distal stent migration in 2 patients and acute cholecystitis due to stent occlusion in 2 patients. The stent occlusions were treated endoscopically[97]. A single step procedure for insertion for lumen opposing metallic stent using AXIOS system has also been reported[98]. EUS guided gallbladder drainage has also been used as an approach for drainage in unresectable pancreatic cancer with use of anti-migratory fully covered metallic stents[99]. EUS guided gall bladder drainage may be of value in situation where a percutaneous procedure is dificult or more risky (presence of ascites and coagulopathy) but comes at an increased risk associated with sedation in patients with various comorbidities and the risk of bile leak.

EUS GUIDED PANCREATIC DUCT DRAINAGE

EUS guided pancreatic ductal (PD) drainage may be indicated for patients with failed transpapillary

drainage like in failed cannulation of non-negotiable strictures in chronic pancreatitis or pancreatic fistulae or pancreaticogastric or pancreaticojejunal stenosis after pancreatic surgery[100]. Both trans-enteric stenting and rendezvous procedures can be accomplished after EUS guided access to the pancreatic duct has been obtained. Once an access has been achieved using EUS-FNA needle and a guidewire is placed into the PD, and dilatation of the tract is done. SEMS are not used to drain the pancreatic duct for the associated risk of obstructive pancreatitis due to blockage of the side branches of the pancreatic duct. Complications associated with EUS guided PD drainage include leakage of pancreatic juice, pancreatitis, perforation or bleeding[101,102]. In a systematic review of 9 studies including 205 patients the pancreatic duct drainage was successful in 58%-100% with clinical success in 74% and a complication rate of 20%[102]. Success rates were lesser in a nationwide retrospective study form Spain[75]. Both rendezvous and transenteric drainage has been reported to have similar efficacy although it may be difficult to do a rendezvous in tight strictures[103,104]. The EUS guided PD access can be utilised for taking brushings to confirm malignancy in pancreatic stricture[105]. Access may be easier to obtain in dilated duct[104]. Some data is available about long term clinical success which indicates that at a median follow-up of 37 mo pain relief was present in 72% patients[106]. Another report indicated complete pain relief in 83% of patients[107]. It is important to suspect underlying malignancy in those with lack of pain relief[108]. Anterograde pancreatic drainage including stricture dilatation and removal of stone has also been reported[109,110]. To summarise EUS guided pancreatic duct drainage can be of use in rescue management of failed ERCP or in patients with surgically altered anatomy but the technique is still evolving and better accessories are needed.

USE OF EUS IN MANAGEMENT OF MALIGNANT DISEASE

Brachytherapy

Recently EUS guided brachytherapy has also been evaluated with radioactive seeds being placed into the tumour of interest under EUS guidance with the help of linear echoendoscope[111,112]. The most popular radioactive seeds are Iodine 125, palladium 103 and iridium 192. In pancreatic cancers where the cells divide quite rapidly, iodine is the radioactive material of choice as it has got a long half life of 60 d. The radioactive spill over the region of interest is definitely an issue of concern but in human tissue the penetration distance of the radiation into surrounding tissue is very small. The seeds of EUS guided brachytherapy were sowed by Sun *et al*[111] with their study in pigs. Sun *et al*[111] published the use of iodine 125 in unresectable pancreatic cancer in 15 patients. The result revealed a median survival of 10.6 mo with 27% patients having partial tumour response[111]. In another study in 22 patients with advanced pancreatic cancer where combination of gemcitabine and Iodine 125 brachytherapy was used, the overall survival rate didn't improve[112].

Fiducial marker placement

For external beam radiation to the cranium, bony landmarks are used for guiding the therapy while in intraabdominal malignancy fiducial markers are placed inside the tumour for guiding therapy. These markers are radioactive spheres, coils or seeds. Earlier fiducials were placed under surgical or radiological guidance but with advent of interventional EUS, these fiducials can be placed under EUS guidance also. Pishvaian *et al*[113] reported EUS guided fiducail placement in 13 patients with technical success achieved in 11/13 patients. An average of 3-4 fiducials were placed in each patient. There have been multiple studies where EUS guided fiducials have been placed successfully in pancreatic cancers, esophageal cancers and neuroendocrine tumours[114-116]. To compare the 2 types of fiducials a study was conducted in 39 patients with advanced pancreatic cancer. Traditional fiducials of 5 mm length and viscoil fiducials of 10 mm length were compared. It was observed that traditional fiducials had better visibility scores as compared to viscoil fiducials and the migration rate between the two types of fiducials was similar[117].

EUS guided ethanol ablation

Ethanol causes cell death by membrane lysis, vascular occlusion and protein denaturation and has been used for ablation of solid and cystic lesions of thyroid, liver, adrenals, *etc*. EUS guided ethanol ablation has been used recently for ablation of pancreatic lesions, neuroendocrine tumors (NETs) and metastatic abdominal lesions. EUS guided fine needle injection therapy using alcohol is safe and better than percutaneous approach as it is delivers alcohol to target tissue with more accuracy, identify surrounding structures and perform injection therapy in real time monitoring.

In a study by Gan *et al*[118] including 25 patients with pancreatic cysts who underwent ablation with variable concentrations of alcohol (5%-80%), the results revealed complete resolution in 8 patients and epithelial ablation in 5 patients who underwent surgery. In another study ethanol injection was compared with saline injection alone. In this study 25/42 patients were initially treated with alcohol and rest 17 with saline. After 3 mo, patients in both the groups were treated with ethanol injection. The results showed that 80% ethanol injection resulted in a greater decrease in size as compared to saline injection. Nine patients who were followed up for 2 years had no recurrence of cyst[119]. In another study of 42 patients with cystic tumours of the pancreas who were initially injected with 99% ethanol followed by paclitaxel. Complete resolution

Table 7 Antitumour agents, their composition and area of use

Name of the agent	Drug	Ref.	Reported use
CYTOIMPLANT	Allogenic mixed lymphocyte culture	Chang *et al*[130]	Advanced pancreatic cancer
TNFerade	cDNA expressing TNF-α (adenovector)	Hecht *et al*[131], Chang *et al*[132] and Citrin *et al*[133]	Pancreatic, esophageal and rectal cancer
ONY X-015	Adenovirus	Mulvihill *et al*[134]	Advanced pancreatic cancer
Oncogel	Paclitaxel and ReGel	Linghu *et al*[135], Matthes *et al*[136] and Vukelja *et al*[137]	Pancreatic, esophageal cancer
Gemcitabine	Gemcitabine	Levy *et al*[138]	Advanced pancreatic cancer
DC's	Dendritic cells	Irisawa[139], Hirooka *et al*[140]	Advanced pancreatic cancer

was achieved in 29 patients. No complications were observed[120]. EUS guided ethanol ablation of pancreatic neuroendocrine tumours has been reported in patients who are not good candidates for surgery either because of age or comorbidities. There have been published reports where even multiple NETs have been injected with alcohol and ablation has been achieved with patient remaining symptom free post injection. But there is a risk of recurrence and metastasis. So long term follow up studies are required to adequately define the role of ethanol ablation in NETs[121-125].

Multiple metastatic lesions have also been ablated with EUS guided ethanol injection but its role in these situations need to assessed in larger studies. These include hepatic metastases from carcinoma colon, pelvic lymph nodal metastases from rectal cancer, left adrenal metastases from non-small cell carcinoma lung, hepatic metastases from pancreatic carcinoma and ablation of a gastrointestinal stromal tumour in a patient whose comorbidities precluded surgery[126-129].

Delivery of antitumor agents

Pancreatic carcinoma has got a poor response to chemotherapeutic agents and radiation. In presence of locally advance disease and borderline resectability, neoadjuvant chemotherapy has been tried, but it carries a poor response rate as the tumour is hypovascular and produces a desmoplastic reaction around it leading to poor delivery of drugs. So various local antitumour agents have been tried in patients with advanced pancreatic carcinoma for palliation and in locally advanced lesions for downstaging before surgery (Table 7).

The problem with all these studies is that they were small and all these agents in this role are still in experimental stage. So we need much more large prospective studies before these techniques can be put into clinical practice.

Tumour ablation

Thermal injury leading to coagulation necrosis has been the principle of radiofrequency ablation (RFA). This principle has been exploited for treatment of solid tumours like hepatocellular carcinoma (HCC) and liver metastases. Percutaneous, open or laparoscopic approach have been associated with morbidity and mortality. Recently EUS guided RFA has been performed under real time guidance in porcine models. Studies of EUS RFA done in porcine models have used the technique for ablation of lymph nodes and pancreatic lesions[141,142]. Majority of pigs tolerated the procedure well except for few complications.

EUS photodynamic therapy

Photodynamic therapy is another modality for tumour ablation. Here a photosensitizer drug is injected and application of light is done to the area of interest. The tumour cells are killed by direct cytotoxic effects, vascular changes and inflammatory reaction[143,144]. A study in porcine models where EUS guided photodynamic therapy has been done to liver, pancreas and kidney showed that 100% necrosis was seen in pancreas only[145].

EUS guided laser therapy

It is an evolving technique and recently a case was reported where EUS guided laser ablation of a left lobe HCC was performed using 22 G needle and patient was followed up for 2 mo with no recurrence of the lesion[146].

EUS-GUIDED INRAABDOMINAL ABSCESS DRAINAGE

EUS guided internal drainage of abdominal and pelvic abscesses has emerged as an alternative to traditional percutaneous drainage. Abscesses in areas close to the gastrointestinal lumen including mediastinum, lesser sac, perihepatic and subphrenic space, and pelvis can be drained using EUS guidance. The procedure involves the usual steps described earlier for PFC drainage: access using 19 G EUS-FNA needle, use of guidewire, dilatation of tract and placement of drainage catheter or pigtail stents. The suggested dilatation diameters for esophagus is 6 mm, for colon and jejunum is 6-8 mm, for duodenum 8-10 mm and in stomach 8-15 mm[147]. Table 8 shows various reports of EUS guided drainage of pelvic abscesses.

Mediastinal abscesses have also been drained under EUS guidance including placement of lumen opposing stents[154,155]. A few reports have also involved aspiration of splenic abscess in setting of pancreatitis[156,157]. Liver abscess have also been drained using EUS guidance

Table 8 Endoscopic ultrasound guided drainage of pelvic abscesses

Ref.	Number	Site	Technical success	Clinical success	Complications
Hadithi *et al*[148]	8	Abdominal (pelvic)	100%	100%	0
Puri *et al*[149]	30	Pelvic (4 prostatic)	93.3%	83.5%	0
Ramesh *et al*[150]	38	11 transcolonic, 27 transrectal	100%	87%	10.5%
Puri *et al*[151]	14	Pelvic	100%	93%	0
Varadarajulu *et al*[152]	25	Pelvic	100%	96%	0
Giovannini *et al*[153]	12	Pelvic	100%	75%	25%

and placement of lumen apposing stent has also been done[158,159].

EUS GUIDED CELIAC PLEXUS BLOCK

Percutaneous celiac plexus neurolysis (CPN) has been used for management of pain in pancreatic cancer and sometimes for chronic pancreatitis. EUS guided CPN has emerged as a more effective technique in recent times[160]. Using the linear echoendoscope at the level of gastroesophageal junction the aorta is located and celiac artery traced. While alcohol is used to obtain CPN, bupivacaine is used for celiac plexus block (CPB). Although triamcinolone is often added to bupivacaine but a randomised study found no benefit with addition of triamcinolone[161]. The average efficacy of CPB for pain relief is around 3 mo. Transient hypotension and diarrhea may occur as side effects of the procedure. The EUS guided technique avoids passage through the vertebrae and muscles at the back as required for a CT guided celiac block and therefore unlikely to have related adverse events like paraparesis[162]. Interestingly, ganglion cells have now been visualised on EUS and it may be better to target ganglions directly[163,164]. In a randomised trial comparing CPN with celiac ganglia neurolysis (CGN), the positive response was higher in the CGN group (73.5% *vs* 45.5%). Half of the patients in CGN group obtained complete relief vis-à-vis 18% in CPN group[165].

Multiple comparative reports have emerged which have compared radiologic *vs* EUS guided CPN. EUS guided CPN provided a more long lasting pain relief (30% up to 24 wk) while with CT guided CPN only 12% had some relief at 12 wk[166]. In a trial comparing one *vs* two injections for pain relief during CPN, no incremental benefit in pain relief was observed with two injections[167]. EUS guided CPB was more efficacious for pain relief in patients with chronic pancreatitis in a randomised comparison with percutaneous CPB[168]. Only a subset of patients with EUS guided CPN obtain complete pain relief and the duration of pain relief is variable. The predictors of pain relief are not established. Also the benefit of performing CPN rather than CPB in chronic pancreatitis is not clear[169].

It is apparent that the availability of interventional EUS has allowed gastroenterologists to make forays into areas which traditionally remained the domain of surgeons and interventional radiologists. With further improvements in accessories and development of EUS-natural orifice transluminal endoscopic surgery, the endosonologist will have to do multiple roles[170].

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MINIREVIEWS

Role of wireless capsule endoscopy in the follow-up of inflammatory bowel disease

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Abstract

The introduction of wireless capsule endoscopy in 2000 has revolutionized our ability to visualize parts of the small bowel mucosa classically unreached by the conventional endoscope, and since the recent introduction of colon capsule endoscopy, a promising alternative method has been available for the evaluation of large bowel mucosa. The advantages of wireless capsule endoscopy include its non-invasive character and its ability to visualize proximal and distal parts of the intestine, while important disadvantages include the procedure's inability of tissue sampling and significant incompletion rate. Its greatest limitation is the prohibited use in cases of known or suspected stenosis of the intestinal lumen due to high risk of retention. Wireless capsule endoscopy plays an important role in the early recognition of recurrence, on Crohn's disease patients who have undergone ileocolonic resection for the treatment of Crohn's disease complications, and in patients' management and therapeutic strategy planning, before obvious clinical and laboratory relapse. Although capsule endoscopy cannot replace traditional endoscopy, it offers valuable information on the evaluation of intestinal disease and has a significant impact on disease reclassification of patients with a previous diagnosis of ulcerative colitis or inflammatory bowel disease unclassified/indeterminate colitis. Moreover, it may serve as an effective alternative where colonoscopy is contraindicated and in cases with incomplete colonoscopy studies. The use of patency capsule maximizes safety and is advocated in cases of suspected small or large bowel stenosis.

Key words: Small bowel capsule endoscopy; Colon capsule endoscopy; Crohn's disease; Ulcerative colitis; Indeterminate colitis; Postoperative; Ileal pouch-anal anastomosis; Refractory pouchitis

Core tip: Wireless capsule endoscopy is a valuable diagnostic tool for the evaluation of lesions located on the small intestine and large bowel mucosa since the recent introduction of colon capsule endoscopy. It plays an important role in the early recognition of recurrence on postsurgical Crohn's disease patients, offers valuable

information on the evaluation of intestinal disease, and aids significantly in patient management, treatment tailoring and disease reclassification in patients with a previous diagnosis of ulcerative or indeterminate colitis. Patency capsule maximizes safety and is advocated in suspected small or large bowel stenosis.

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INTRODUCTION

The follow-up of patients with known inflammatory bowel disease consists in close disease monitoring for the maintenance of clinical remission, early detection of biochemical or clinical relapse and early recognition, as well as prevention, of disease and treatment related complications. Since various studies[1-4] have provided strong evidence that the inflammation of the intestinal mucosa is not firmly associated with patients' symptoms and laboratory markers of inflammation, the treatment goal has evolved to a new concept, the achievement and maintenance of deep remission. Its definition includes the concurrent abatement of symptoms, a score < 150 as measured with Crohn's Disease Activity Index (CDAI), mucosal healing, a term referring to the endoscopic restoration of normal mucosal appearance of a previously inflamed region and the complete absence of ulceration as well as macroscopic and histological signs of inflammation[5], and diminution of inflammatory markers. In the absence of a consensus on mucosal healing definition in ulcerative colitis patients, this could involve the disease's clinical and endoscopic remission[6-8]. In Crohn's disease patients, deep remission is associated with a better health-related quality of life and minimization of disease related complications requiring hospitalization or surgery[6].

Despite its invasive character, colonoscopy is considered the gold standard method for the evaluation of intestinal mucosa lesions as it provides accurate assessment of disease extension and localization, offering the ability of tissue sampling of abnormal mucosal segments. By contrast to colonoscopy, the introduction of wireless capsule endoscopy in 2000[9], a non-invasive well-tolerated diagnostic method, allowed the visualization of parts of the small intestine beyond the reach of conventional endoscopes and also the large bowel mucosa, since the recent introduction of wireless colon capsule endoscopy. Current research does not support the use of colon capsule endoscopy over colonoscopy for the evaluation of mucosal healing and disease activity[10] although results of a recent study[11] demonstrate that colon capsule endoscopy findings can result in changes of the initial diagnosis, in favor of Crohn's disease. The aim of this review is to evaluate the importance of wireless capsule endoscopy in mucosal healing assessment, treatment management and disease reclassification of inflammatory disease patients, their follow-up in the post-operative period, as well as to highlight its possible future roles.

CAPSULE ENDOSCOPY: BENEFITS, DRAWBACKS, LIMITATIONS AND SAFETY

Capsule endoscopy is a non-invasive, well-tolerated method, allowing direct visualization of the small bowel mucosa and having a significant higher diagnostic yield compared to other diagnostic methods[12].

Its main disadvantages (Table 1) are the procedure's higher cost compared to other modalities, the inability of tissue sampling, the significant incompletion rate which in several trials[13-15] is reported to range from 15% to 30%, the risk of aspiration and the risk of capsule retention, which in Crohn's disease patients is estimated to be 2.6%[15] and may require surgery for the removal of the retained capsule.

The use of capsule endoscopy is contraindicated in patients with known stricturing or obstructing disease and in selected cases, radiology may still be necessary to exclude the presence of strictures. It is considered to be a safe technique[16] and the administration of a dissolvable patency capsule to patients with suspected strictures prior to the procedure, provides adequate assessment of the gastrointestinal patency and maximizes safety[17,18]. In cases of known gastroparesis or in patients unable of swallowing, the videocapsule can be administered endoscopically. The relative contraindication of wireless capsule administration in patients with electromedical devises is in question, as according to recent research[19] it is considered safe.

CAPSULE ENDOSCOPY SCORING INDEXES FOR THE ASSESMENT OF MUCOSAL INFLAMMATION

In an effort to maximize objectivity on the interpretation of small bowel capsule endoscopy findings and the need of a common language to report severity of small bowel inflammation, two diagnostic scoring systems have been developed, Lewis score (LS) and Capsule Endoscopy Crohn's Disease activity Index (CECDAI).

Developed by Gralnek *et al*[20] in 2008, LS[20], an incorporated feature of Given's Rapid Reader software, offers a quantitative assessment of inflammation severity using the Capsule Endoscopy Structured Terminology[21] for the description of lesions and a grading system for the assessment of inflammation severity. Capsule transit time is used to divide the small bowel in three tertiles and based on the severity of 3 endoscopic variables - villous edema, ulcers and stenosis - each tertile score is calculated individually. The final score ranges from 8 to 4800 points and is the sum of the tertile with the

Table 1 Advantages and disadvantages of wireless capsule endoscopy

Advantages
Non-invasive well-tolerated method
Allows direct visualization of distal and proximal parts of the small bowel (SBCE) and large bowel mucosa(CCE)
Disadvantages
High cost compared to other modalities
Inability of tissue sampling
Significant incompletion rate (15%-30%)
Risk of capsule retention (2.6%)
Risk of aspiration

SBCE: Small bowel capsule endoscopy; CCE: Colon capsule endoscopy.

greatest score added to the stenosis score. A score below 135 points represents a normal appearing mucosa or clinically insignificant findings.

CECDAI, a quantitative method developed by Gal *et al*[22] in 2008, employs the variables of inflammation, extent of disease and the presence of strictures as well as a grading system for the assessment severity. Small bowel is divided in proximal and distal segments after the midpoint determination with the use of small bowel transit time. Segmental scores are gauged separately by multiplying the inflammation score by the extent-of disease score and adding the stricture score. The sum of segmental scores represents the final CECDAI score. Both scores should be interpreted with regard to the patient's history, as they cannot identify the underlying reason of mucosal inflammation. The use of LS and Capsule Endoscopy Crohn's Disease Activity Index is advocated, as they provide an objective non-invasive method for the evaluation of small bowel inflammation and follow up of Crohn's disease[22-24] and correlate closely with highly sensitive markers of intestinal inflammation such as fecal calprotectin[25], a protein released from neutrophils and inflamed mucosa. Fecal calprotectin is not able to determinate the cause of intestinal inflammation, however fecal calprotectin levels are demonstrated to correlate closely with intestinal inflammation[26-29] and are proved to be a valuable selection tool prior to capsule endoscopy studies as despite the presence of symptoms, patients with fecal calprotectin levels between 50 and 100 μg/g, are shown to have negative for findings studies[30].

THE ROLE OF WIRELESS CAPSULE ENDOSCOPY IN THE ASSESSMENT OF MUCOSAL HEALING AND TREATMENT TAILORING

Clinical remission is not strongly associated with the diminution of inflammatory markers[4] although C-reactive protein (CRP) is demonstrated to be a useful marker in the evaluation of moderate to severe Crohn's disease[31]. Moreover, clinical and laboratory improvement of patients under treatment is not associated with mucosal healing[31]. Patients continue to have small bowel aphthous ulcerations in video capsule endoscopy studies (Table 2) one month after clinical remission and it is estimated that approximately 6 mo are necessary for the complete endoscopic restoration of small bowel mucosa[4,32]. In a multicenter prospective study[3] including 40 patients with known or suspected non-stricturing, non-penetrating Crohn's disease, only one third of the patients who achieved clinical response improved their endoscopic image in capsule endoscopy studies. A cohort of 43 patients with symptomatic small bowel Crohn's disease, under biologic or immunomodulatory treatment, evaluated mucosal healing and deep remission rate on baseline and after 12 and 52 wk on treatment[1,33]. Their baseline demographics, quality-of-life questionnaires, Harvey-Bradshaw index, CRP and fecal calprotectin levels were collected and Capsule Endoscopy Crohn's Disease Activity Index was used to assess ileitis severity. Active small bowel Crohn's disease was present in 39 patients (90%) on baseline and 28 patients (65%) had an endoscopic re-assessment during week 52. Despite the clinical and biochemical improvement, no patient achieved complete mucosal healing on week 12[1]. Twelve patients achieved deep remission on week 52 (42%)[33]. The correlation between capsule endoscopy findings, clinical symptoms (Crohn's Disease Activity Index and Inflammatory Bowel Disease Questionnaire) and laboratory markers of inflammation (CRP) was evaluated in 19 patients with known, moderately active Crohn's disease under treatment[2]. All patients had a proven functional patency to minimize the risk of capsule retention, and small bowel capsule endoscopy studies at baseline, after 4, 12 and 24 wk on treatment. Mucosal inflammation was evaluated with the use of LS. At baseline, no correlation was found between clinical symptoms, markers of inflammation and LS, and capsule endoscopy findings were not associated with patients' symptoms on 4 and 12 wk of treatment, leading to the conclusion that capsule endoscopy is a reliable, independent and objective diagnostic modality for the assessment of mucosal healing and response to therapy, and on the prognosis of prolonged clinical disease remission[32]. In addition, data obtained of two recent retrospective studies[34,35] indicate that capsule endoscopy findings assist on decision making, treatment changes or initiation of new pharmaceutical agents, in a significant proportion of inflammatory bowel disease patients.

THE ROLE OF WIRELESS CAPSULE ENDOSCOPY IN THE POSTOPERATIVE PERIOD OF INFLAMMATORY BOWEL DISEASE PATIENTS

Recurrence

The introduction of biologic therapy for the treatment of inflammatory bowel disease did not eliminate

Table 2 Key studies describing the role of wireless capsule endoscopy on the assessment of mucosal healing in Crohn's disease patients under treatment

	Ref.	Treatment	Indication	Patients (*n*)	Conclusion
CD	Niv *et al*[2]	Yes	SB mucosa evaluation of known CD patients	19	Musocal findings are independent from clinical and laboratory parameters
CD	Hall *et al*[1]	Yes	SB mucosal healing and deep remission rates assessment on 12 wk of treatment of known symptomatic CD patients	43	Symptomatic and biochemical response to treatment is not mirrored by mucosal healing
CD	Hall *et al*[33]	Yes	SB mucosal healing and deep remission rates assessment on 52 wk of treatment of known symptomatic CD patients	43	Symptomatic and biochemical response to treatment appears to be mirrored by endoscopic remission in 42% of individuals
CD	Efthymiou *et al*[3]	Yes	SB mucosal healing assessment of known symptomatic CD patients	40	Clinical response does not correlate closely with mucosal healing in patients with CD of the small bowel
CD	Tsibouris *et al*[32]	Yes	Assessment of detection rate of small bowel ulcerative lesions and completion rate in CD patients in acute phase and remission	102	SB aphthous ulcers are present a month after entering clinical remission

CD: Crohn's disease; SB: Small bowel; CRP: C-reactive protein.

the need for surgical intervention[36-40]. Eventually, 20%-30% of ulcerative colitis patients[41,42] and up to 75% of Crohn's disease patients[43], will require surgery for the management of uncontrolled inflammatory bowel disease and disease related complications. A common and undesirable postsurgical outcome is the development of disease recurrence. In Crohn's disease patients, recurrence rate increases with time[44] and is demonstrated to be higher in smokers[45], patients with ileocolonic involvement[46], perforating disease[47] and 5-ASA-treated patients with end-to-end anastomosis[44]. The introduction of Rutgeerts endoscopic scoring system[48] has provided a valuable modality for the quantified assessment of postoperative recurrence of the ileocolonic anastomosis or neoterminal ileum, and a valuable prognostic tool of Crohn's disease recurrence[48-50], since endoscopic recurrence precedes the development of symptoms[48] and does not correlate with CDAI[51]. The follow-up of postoperative patients is directed towards recognition of endoscopic recurrence (Table 3), as severe endoscopic recurrence rate is estimated at 50.2% (95%CI: 28-73; range: 30-79) and early identification and initiation of treatment may prevent clinical recurrence[52,53].

In a prospective study of 22 Crohn's disease patients, capsule endoscopy was reported to have comparable results with other noninvasive tests on the detection of recurrence[54]. Moreover, based on the results of a prospective study[55] including 35 patients who had undergone ileocolonic or partial ileal resection, wireless capsule endoscopy was not shown to be superior to ileocolonoscopy for the detection of recurrence on the neoterminal ileus although it enabled the visualization of lesions beyond colonoscope's reach in two out of three patients and aided significantly in the detection of recurrence in two patients missed by ileocolonoscopy. However, capsule endoscopy was the diagnostic modality preferred by patients in a small prospective study[56] including 24, symptom-free Crohn's disease patients under no prophylactic treatment, who had undergone ileocolonic anastomosis. In the same study, the authors concluded that capsule endoscopy was more effective in the detection of a significant number of Crohn's disease recurrence missed by colonoscopy and an effective diagnostic alternative for the visualization of the neoterminal ileum of patients with incomplete colonoscopy studies. Current research supports the use of baseline capsule endoscopy, shortly after the resection, for the detection of true cases of recurrence, as many ulcerations near the anastomotic site are formed due to factors related to surgery, such as disturbed blood flow and sutures[57], but its preoperative use is reported to be of little value for the prognosis of recurrence[58]. The use of wireless capsule endoscopy in suspected or known luminal stenosis is contraindicated[54,57].

Anemia

Based on the results of a small study of 17 ulcerative colitis patients with ileal pouches and persistent iron deficiency anemia[59], the authors concluded that wireless capsule endoscopy is a well-tolerated procedure to provide additional information on the reason of anemia. Patients with persistent anemia, 12 mo after ileal pouch-anal anastomosis (IPAA) or continent ileostomy, were evaluated with upper gastrointestinal endoscopy, pouch endoscopy and videocapsule endoscopy, and they had laboratory screening to exclude celiac disease. The reason of anemia was identified in 5 patients (29.4%). In one patient, arterio-venous malformations of the small bowel were only recognized by capsule endoscopy.

Pouchitis in patients with IPAA

Surgical removal of the colon and rectum with the creation of an artificial pouch, the IPAA, may be the only treatment option for ulcerative colitis patients with medically uncontrolled disease, who are unwilling to receive immunomodulatory or biologic therapy, or suffering from severe disease complications.

Table 3 Key studies on the role of wireless capsule endoscopy on postoperative Crohn's disease recurrence

Patient group	Ref.	No. of patients	WCE findings/(*n*)	Ileocolonoscopy findings/(*n*)
CD	Bourreille *et al*[55]	32	21/(32)	19/(32)
CD	Pons Beltrán *et al*[56]	24	15/(22)	6/(19)
CD	Biancone *et al*[54]	22	16/(17)	21/(22)
CD	Kono *et al*[57]	19	14/(18)	NA

CD: Crohn's disease; WCE: Wireless capsule endoscopy; WCE findings: Number of patients with findings on WCE; WCE (*n*): Total number of patients who had undergone WCE; Ileocolonoscopy findings: Number of patients with findings on ileocolonoscopy; Ileocolonoscopy (*n*): Total number of patients who had undergone ileocolonoscopy; NA: Not available.

Pouchitis is the most common complication, with a cumulative probability of nearly 50% ten years after IPAA performed[60] requiring investigation for the recognition of the underlying cause.

Results based on trials of ulcerative colitis patients with IPAA and symptomatic pouchitis[35,61,62] (Table 4), support the use of capsule endoscopy for the evaluation of small bowel mucosa on the suspicion of Crohn's disease and on differentiating intermediate colitis.

THE ROLE OF WIRELESS CAPSULE ENDOSCOPY ON DISEASE RECLASSIFICATION

Inflammatory bowel disease patients may undergo multiple imaging studies, endoscopic procedures and biopsies before reaching a definitive Crohn's disease or ulcerative colitis diagnosis, while 10%-15% of patients will remain unclassified[63]. Capsule endoscopy has become an important tool for the reclassification of disease (Table 5) in patients with an initial diagnosis of ulcerative colitis or inflammatory bowel disease unclassified/indeterminate colitis. The importance of wireless capsule endoscopy in the diagnostic workup of inflammatory bowel disease was demonstrated in a recent study of 23 known ulcerative colitis patients[64] where small bowel lesions (13 patients, 57%) and erosions (8 patients, 35%) were identified in the majority of them.

Corresponding results from the initial experience with small bowel capsule endoscopy[65] have demonstrated that the identification of small bowel lesions by wireless capsule in patients with isolated colitis, lead to further investigation with ileocolonoscopy with biopsies, and a change of diagnosis in favor of Crohn's disease. In a retrospective trial[62] including 120 patients with known ulcerative colitis or indeterminate colitis undergone capsule endoscopy, 19 patients (15.8%) had findings suggestive of small bowel Crohn's disease involvement. Interestingly, patients with the highest proportion of small bowel disease were those with a history of colectomy (7 out of 21 patients, 33%) compared to the patients who did not undergo colectomy (12 out of 99 patients/12%), indicating the importance of capsule endoscopy studies prior to colectomy in ulcerative colitis patients. Similarly, data obtained from a study of 30 inflammatory bowel disease unclassified patients with negative serology[66] showed that wireless capsule endoscopy findings resulted in disease reclassification in favor of Crohn's disease in five of them. Another significant conclusion of this study was that negative for findings capsule endoscopy studies, do not exclude small bowel Crohn's disease, as further investigation with ileocolonoscopy and biopsies in six patients led to a diagnosis of Crohn's disease in five patients and ulcerative colitis in one patient. In two studies that enrolled pediatric patients[67,68] capsule endoscopy resulted in reclassification of more than half of the ulcerative colitis, inflammatory bowel disease unclassified/indeterminate colitis patients to Crohn's disease.

Table 4 Key studies on the role of wireless capsule endoscopy on pouchitis patients

Patient group	Ref.	No. of patients	WCE findings/(*n*)	CD reclassification
UC (IPAA)	Calabrese *et al*[61]	16	15/(15)	None
UC (IPAA)	Mehdizadeh *et al*[62]	21	7/(21)	7
UC (IPAA)	Long *et al*[35]	23	13/(23)	3

UC: Ulcerative colitis; IPAA: Ileal pouch-anal anastomosis; WCE findings: Number of patients with findings on WCE; WCE (*n*): Total number of patients who had undergone WCE; CD: Crohn's disease; WCE: Wireless capsule endoscopy.

POSSIBLE FUTURE INDICATIONS OF WIRELESS CAPSULE ENDOSCOPY IN THE FOLLOW UP OF INFLAMMATORY BOWEL DISEASE PATIENTS

Research on the prognostic value of mucosal healing on treatment response[69-72], has shown that assessment of mucosal healing on certain time points can predict the likelihood of prolonged deep remission. The data of 127 patients[73] who had participated in the SONIC trial, were used to estimate the prognostic value of ileocolonoscopy findings on treatment response. Patients Simple Endoscopic Score for Crohn's Disease and the Crohn's Disease Endoscopic Index of Severity were calculated on baseline, after week 26 and week 50. Namely, the endoscopic response and mucosal healing in week 26 identified the patients who would be on corticosteroid-free clinical remission on week 50. The study's results provided confirmatory evidence that assessment of mucosal healing in certain time points during therapy has a significant prognostic value on the response of treatment.

Growing evidence[74-76] in the corresponding literature, indicate the strong association between disease location and disease complications. Patients with ileal

Table 5 Key studies evaluating the role of wireless capsule endoscopy on disease reclassification

Patient group	Ref.	No. of patients	SB findings of inflammation	Reclassified to CD
UC/IC	Gralnek *et al*[68]	4	2	2
UC	Higurashi *et al*[64]	23	13	None
UC/IC	Cohen *et al*[67]	7	5	5
UC/IBDU	Mehdizadeh *et al*[62]	120	19	NA
IBDU	Maunoury *et al*[66]	30	5	5
UC/IC	Mow *et al*[65]	21	12	5

UC: Ulcerative colitis; IC: Indeterminate colitis; IBDU: Inflammatory bowel disease unclassified; SB: Small bowel; CD: Crohn's disease; NA: Not available.

Crohn's disease were shown to have a greater risk of stricturing and penetrating disease development as well as disease progression compared to those with colonic involvement.

There is no supporting evidence for the use of wireless capsule endoscopy on treatment response, on risk stratification and as a prognostic tool for prolonged remission, but given videocapsule endoscopy's non invasive nature and the advantage of detailed imaging of the entire small intestine, it could be a promising tool towards this direction.

Wireless capsule endoscopy could play an important role in the early detection of ulcerative colitis related panenteritis[77], a new and rare entity related to colectomy which typically occurs after colectomy, and its histological picture is not compatible with Crohn's disease. In a small case series of 6 patients[78], the use of ileocolonoscopy identified ulcerative colitis related panenteritis findings in 5 patients, resulting in treatment step-up and clinical improvement. One patient had to be evaluated with capsule endoscopy to confirm small bowel mucosa inflammation leading to the conclusion that video capsule endoscopy could offer an alternative method for the early detection of this rare complication.

CONCLUSION

Wireless capsule endoscopy is a valuable, non-invasive tool for the follow-up of inflammatory bowel disease, offering direct and detailed visualization of the entire intestine. Even though it cannot replace the role of traditional endoscopy, its use is advocated when there is high suspicion of small bowel disease involvement and as an alternative method in incomplete colonoscopy studies or when colonoscopy is contraindicated. Wireless capsule endoscopy's important disadvantages comprise the inability of tissue sampling and the limited, or in selected cases, prohibited application on patients with known stenosis or obstruction of the intestinal lumen, due to the high risk of capsule retention. Unnecessary capsule endoscopy studies can be avoided with the use of fecal calprotectin levels to identify patients who will probably not benefit from the procedure, and the use of patency capsule to identify patients that are likely to experience capsule retention. Lewis Score and Capsule Endoscopy Crohn's Disease Activity Index are validated, objective and reliable scoring systems developed to minimize interobserver agreement and provide a standardized reporting system of small-bowel inflammation. Assessment of mucosal inflammation has a positive impact on treatment tailoring and is proven to be a reliable prognostic tool for disease remission. Videocapsule endoscopy studies in the postoperative period of ulcerative colitis and inflammatory bowel disease unclassified/indeterminate colitis patients provide valuable information on the differential diagnosis of Crohn's disease as well as postoperative complications, and can aid significantly in the early recognition of recurrence for the timely initiation of immunomodulatory or biologic treatment, before obvious clinical and laboratory relapse. Wireless Capsule endoscopy may have potentially significant roles in the prognosis of treatment response as well as the occurrence of potential complications and the early diagnosis of ulcerative colitis related panenteritis, a recently described rare entity, affecting patients with ulcerative colitis after colectomy.

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ORIGINAL ARTICLE

Retrospective Study

Role of double-balloon enteroscopy in malignant small bowel tumors

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Author contributions: Pérez-Cuadrado Robles E, Esteban Delgado P and Bebia Conesa P contributed equally to this work; Martínez Andrés B, Franulic Guggiana M, Alcaraz Mateos E and Fernández Caballero M designed and performed the research; Rodrigo Agudo JL and Chacón Martínez S analyzed the data; Latorre R, Soria F, Herrerías Gutiérrez JM and Pérez-Cuadrado Martínez E wrote the paper.

Ethics approval: This study was a retrospective and descriptive study without prospective interventions or control group. Thus, we have not considered necessary to submit the manuscript to the Institutional Review Board.
Informed consent: All patients provided written consent to undergo DBE under general anesthesia or deep sedation. However, in this retrospective study of 627 patients with a long span of time (2004-2014) the informed consent to be enrolled in the study was waived. All data are anonymized and there were no prospective interventions.
Conflict-of-interest: None to declare.
Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at kikemurcia@gmail.com. Consent was not obtained but the presented data are anonymized and risk of identification is low.

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Abstract

AIM: To assess the double-balloon enteroscopy (DBE) role in malignant small bowel tumors (MSBT).

METHODS: This is a retrospective descriptive study performed in a single center. All consecutive patients who underwent a DBE with final diagnosis of a malignant neoplasm from 2004 to 2014 in our referral center were included. Patient demographic and clinical pathological characteristics were recorded and reviewed. MSBT diagnosis was achieved either by DBE directed

biopsy with multiple tissue sampling, endoscopic findings or histological analysis of surgical specimen. We have analyzed double-balloon enteroscopy impact in outcome and clinical course of these patients.

RESULTS: Of 627 patients, 28 (4.5%) (mean age = 60 ± 17.3 years) underwent 30 procedures (25 anterograde, 5 retrograde) and were diagnosed of a malignant tumor. Patients presented with obscure gastrointestinal bleeding (*n* = 19, 67.9%), occlusion syndrome (*n* = 7, 25%) and diarrhea (*n* = 1, 3.6%). They were diagnosed by DBE biopsy (*n* = 18, 64.3%), histological analysis of surgical specimen (*n* = 7, 25%) and unequivocal endoscopic findings (*n* = 2, 7.1%). Gastrointestinal stromal tumor (*n* = 8, 28.6%), adenocarcinoma (*n* = 7, 25%), lymphoma (*n* = 4, 14.3%), neuroendocrine tumor (*n* = 4, 14.3%), metastatic (*n* = 3, 10.7%) and Kaposi sarcoma (*n* = 1, 3.6%) were identified. DBE modified outcome in 7 cases (25%), delaying or avoiding emergency surgery (*n* = 3), modifying surgery approach (*n* = 2) and indicating emergency SB partial resection instead of elective approach (*n* = 2).

CONCLUSION: DBE may be critical in the management of MSBT providing additional information that may be decisive in the clinical course of these patients.

Key words: Double balloon enteroscopy; Malignant small bowel tumors; Obscure gastrointestinal bleeding; Gastrointestinal stromal tumor; Occlusion syndrome

Core tip: Malignant small bowel tumors (MSBT) are a heterogeneous and relatively rare group of neoplasms. Double balloon enteroscopy (DBE) may have a critical role in the management of MSBT because of its diagnosis and therapeutic capabilities. DBE procedure may delay or avoid emergency surgery, clarifying the tumor location and characteristics. We have assessed DBE impact in these lesions in a large series of patients of a single referral center.

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INTRODUCTION

Small bowel tumors (SBT) are relatively rare, accounting for 3% to 6% of all gastrointestinal neoplasms[1]. Malignant SBTs (MSBT) are described in the 3.6%-14.5% of patients of double balloon enteroscopy (DBE) series[2-4]. The difference in incidence in these studies is because many authors considered benign and malignant tumors and included duodenal neoplasms. MSBT are a heterogeneous group with different predominant histological types within different studies[5-10]. We will focus on malignant primitive SB tumors such as adenocarcinoma, stromal, neuroendocrine, lymphoproliferative and metastatic tumors. Moreover, these lesions may have a poor prognosis in its natural course so that early diagnosis and treatment may be critical[11,12]. These tumors are often diagnosed late because of their nonspecific clinical presentation[13-16], when they have few therapeutic possibilities[17,18].

Obscure gastrointestinal bleeding (OGIB) is the most common clinical presentation in some studies[4,19,20], while a suspected mass is reported to be the first DBE indication by other authors[2,21]. Therefore, MSBT represent a real diagnostic challenge for the physician. DBE is a well-established procedure in diagnosis and treatment of SB disorders. However, there are few data to date reporting DBE role in MSBT[20,22-24]. Our study was conducted to assess the impact of DBE in these neoplasms.

MATERIALS AND METHODS

This is a retrospective descriptive study. All consecutive patients with MSBT who underwent a DBE procedure in our institution were investigated. Patient demographic and clinical pathological characteristics were recorded. MSBT diagnosis was achieved either by DBE directed biopsy with multiple tissue sampling, endoscopic findings or histological analysis of surgical specimen.

DBE procedure

DBE procedure (Fuji Film, Saitama, Japan) was performed by expert endoscopists as described by Yamamoto *et al*[25]. Fujinon EN-450 P5, EN-450 T5 and EN-580T enteroscopes were used. There was no special preparation for the anterograde approach besides an 8-12 h fast. For the retrograde approach, bowel preparation was performed as in colonoscopy. All patients provided written consent to undergo DBE under general anesthesia or deep sedation. Capsule endoscopy (CE) and radiological studies such as CT scan were also considered, when available.

Endoscopists were aware of prior findings reported by CE or other techniques. DBE approach was selected based on the information prior to DBE procedure including previous CE, clinical and/or radiological findings. When the location was uncertain, the oral approach was preferred.

DBE data including indication, approach, endoscopic findings, tumor location, time of the procedure, biopsy histological diagnosis, therapeutics and complications were collected. Tattoo injection was performed to mark the maximum length of bowel inspected or the location

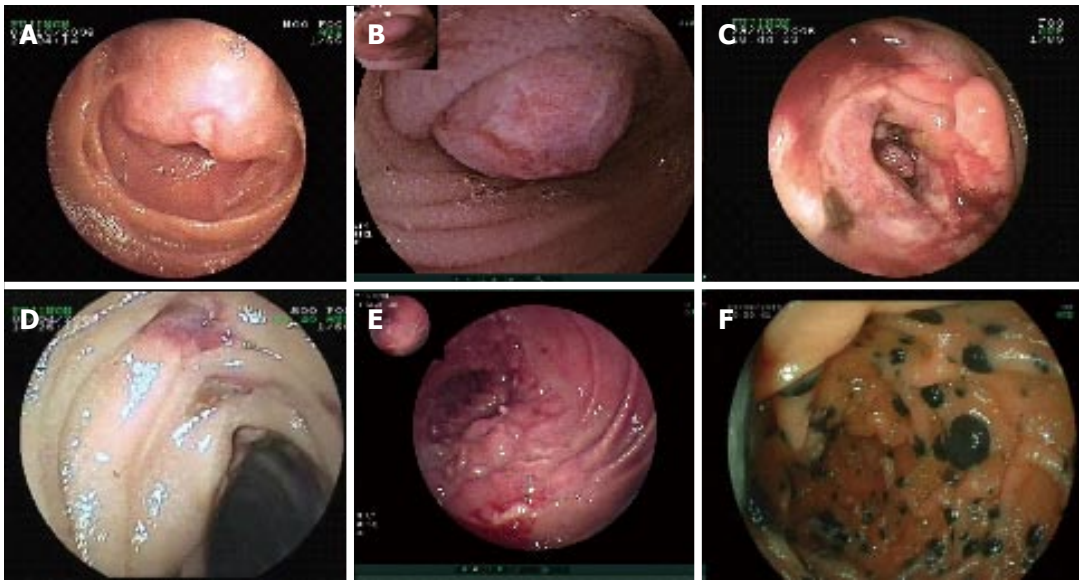

Figure 1 Endoscopic images of different types of malignant small bowel tumors. A: Ulcerated jejunal gastrointestinal stromal tumor; B and C: Stenosing adenocarcinomas; D: Kaposi sarcoma; E: Mucosa-associated lymphoid tissue lymphoma; F: Melanoma.

of the lesion and to guide the elective or emergency surgery.

Finally, we analyzed how DBE procedure influenced MSBT management and outcome. In this sense, avoiding or modifying the elective or emergency surgery approach was considered as the main evaluation criterion.

Descriptive statistics were used to describe clinical pathological features, endoscopic and radiological findings. Categorical variables were calculated as percentages and continuous variables were expressed as mean values (SD).

RESULTS

Of 627 consecutive patients who underwent 880 DBEs from January 2004 to September 2014 at our referral center, 89 (14.2%) were confirmed to have a SBT. Twenty-eight patients (4.5%) (mean age ± SD: 60 ± 17.3 years) underwent 30 DBEs (25 anterograde, 5 retrograde) (median time: 65 min, range 20-160) and were diagnosed of a MSBT. We only include the malignant tumors localized distal to Treitz. There was a male preponderance in gender (*n* = 20, 71.4%).

Patient's characteristics are shown in Table 1. The most common clinical indication was OGIB (67.9%). Patients presented with overt-OGIB (*n* = 9, 32.1%), occult-OGIB (*n* = 10, 35.7%), occlusion syndrome (*n* = 8, 28.6%) and diarrhea (*n* = 1, 3.6%). In addition, 10 patients (35.7%) had weight loss and 6 patients (21.4%) transfusion requirements.

DBE was indicated following CE in 17 cases (60.7%) and this procedure confirmed the MSBT in 14 cases (82.4%). The capsule was retained in 4 cases due to SB stenosis identifying the tumor in two of them and retrieved by DBE in all patients. CT scan (*n* = 8, 28.6%) and other radiological studies (*n* = 2, 7.1%) were previously performed and a suspected mass was identified in 6 cases (21.4%). CT scan also detected a SB complete stenosis in four cases and DBE clarified that only in three of them there was a complete stenosis without overpassing it with the endoscope. Among patients with obstructive symptoms, radiological imaging was the first SB study in 6 (75%) cases and direct DBE was performed in 2 (25%) patients.

DBE directed-biopsy was attempted in 25 patients (89.3%) and benign/reactive mucosa was found in 5 of them (1 midgut neuroendocrine tumor, 1 adenocarcinoma and 3 GIST) so that 20 patients (71.4%) were finally confirmed to have a MSBT by DBE biopsy (Table 2). Two patients (7.1%) had moderate bleeding after DBE biopsy that stopped after endoscopic treatment. Directed-biopsy by DBE was not attempted in 3 patients (10.7%) with GIST (*n* = 1), neuroendocrine tumor (*n* = 1) and metastatic disease (*n* = 1) because of active bleeding that required emergency surgery within GIST and neuroendocrine tumors and because it was considered unnecessary for diagnosis in the other case. In addition, histological analysis of surgical specimen and endoscopic findings lead to diagnosis in 7 (25%) and 1 (3.6%) patients, respectively.

Seven different histological types of MSBT were found. Most of them were located in jejunum (*n* = 20, 71.4%) followed by ileum (*n* = 8, 28.6%). We have only included malignant tumors located between distal to Treitz and terminal ileum. Endoscopic findings of different MSBT are shown in Figure 1.

The most common malignant tumor was GIST (*n* = 8, 28.6%) followed by adenocarcinoma (*n* = 7, 25%). GIST was also the most common MSBT within OGIB patients (36.8%). In two GIST an enteric fistula was identified by DBE with passage of contrast into the peritoneum so that emergency surgery was indicated after tattoo injection. One of them deceased

Table 1 Patient characteristics by histological type of malignant small bowel tumor

	GIST	Adenocarcinoma	Lymphoma	Neuroendocrine tumor
No. patients (% of MSBT)	8 (28.6%)	7 (25%)	4 (14.3%)	4 (14.3%)
Sex (M/F)	7/1	3/4	2/2	4/0
Mean age (SD) (yr)	64 ± 15	59 ± 16	48 ± 22	55 ± 24
Clinical presentation				
Overt-obscure OGIB	4	1	1	1
Occult-obscure OGIB	3	3	2	2
Diarrhea	0	0	0	1
Occlusion syndrome	1	3	1	0
Duodenum/jejunum/ileum	0/7/1	0/6/1	0/3/1	0/0/4

MSBT: Malignant small bowel tumor; GIST: Gastrointestinal stromal tumor; OGIB: Obscure gastrointestinal bleeding.

in the intensive care unit. Another patient with severe anemia and transfusion requirements underwent a DBE that confirmed an ulcerated jejunal GIST with active bleeding. Argon plasma coagulation was successfully performed so that emergency surgery was delayed. The positive detection rate by directed-biopsy within GIST was 57.1%.

Adenocarcinoma was mainly located in jejunum (*n* = 5, 71.4%). One patient underwent DBE because of one CT suspected jejunal mass and chronic anemia. Finally two synchronic jejunal adenocarcinomas were found modifying the surgery approach. Three patients with adenocarcinoma (42.9%) had impassable SB stenosis despite multiples endoscopic maneuvers and an enteral stent was successfully placed in one case[26]. There were 2 patients with liver metastasis at diagnosis and 3 patients did not underwent surgery because of comorbidities. Finally, 4 patients (57.1%) with adenocarcinoma underwent elective surgery.

Among lymphoma tumors (*n* = 4, 14.3%), there were 2 MALT, 1 non-Hodking diffuse large B lymphoma and 1 Burkitt lymphoma. One patient with a jejunal MALT lymphoma had refractory celiac disease. Three patients were treated by chemotherapy and the remaining patient refused treatment.Half of patients (*n* = 2) with neuroendocrine tumors had multiple small tumors besides the main ileal lesion undiagnosed by previous enhanced CT scan.

A jejunal Kaposi sarcoma actively bleeding was identified in a patient with acute overt-OGIB and endoscopic hemostasis was successfully performed. All patients with SB metastasis had the primary lesion already diagnosed (colonic adenocarcinoma, choriocarcinoma, lung adenocarcinoma and melanoma). DBE modified surgical approach in one patient with

Table 2 Final diagnosis and histological analysis by double balloon enteroscopy directed-biopsy

	DBE biopsy	Final diagnosis (% of MSBTs)
MSBT	20/25 (80%)	28
GIST	4/7 (57.1%)	8 (28.6%)
Adenocarcinoma	6/7 (85.7%)	7 (25%)
Lymphoma	4/4 (100%)	4 (14.3%)
Neuroendocrine tumor	2/3 (66.7%)	4 (14.3%)
Metastatic	3/3 (100%)	4 (14.3%)
Kaposi Sarcoma	1/1 (100%)	1 (3.6%)

DBE: Double balloon enteroscopy; MSBT: Malignant small bowel tumor; GIST: Gastrointestinal stromal tumor.

clinical occlusion syndrome suspected because of metastasis in whom a total DBE confirmed that the obstruction was due to adherences.

Tattoo injection was performed in 21 cases (75%) and guided elective (*n* = 8, 28.6%) or emergency surgery (*n* = 5, 17.9%). There was no complication related to therapeutics.

In summary, DBE modified the clinical course and outcome in 7 patients (25%), delaying or avoiding emergency surgery (*n* = 3), modifying surgery approach (*n* = 2) and indicating emergency SB partial resection instead of elective approach (*n* = 2). It's interesting to note that within these 7 patients, in only 3 cases (42.9%) surgery was delayed or avoided due to endoscopic therapy. Two patients with actively bleeding GIST and Kaposi sarcoma in whom argon plasma coagulation was successfully performed and one patient with a stenosing adenocarcinoma who underwent a DBE with an enteral prosthesis placed.

DISCUSSION

Regarding the diagnostic performance of deep enteroscopy in SB tumors, Chen *et al*[3] in an Asiatic retrospective study reported 440 DBEs in 400 patients, diagnosing 67 SB tumors by DBE, with 16.8% overall diagnostic yield. Eleven patients with negative DBE were diagnosed of a SBT by CE or surgery. The positive detection rate among the 78 patients with SBT was higher with DBE than with CT scan (85.9% *vs* 72.9%, respectively). Adenocarcinoma (29.5%), GIST (24.4%) and lymphoma (15.4%) were the most common tumors reported by this author. They were mostly located at the jejunum (60.3%), and the MSBT detection rate was 14.5%. Cangemi *et al*[2], in an American research study, with 1652 DBE performed in 1106 patients reported a SBT detection rate of 12.1%. However, the MSBT rate was about 5%. The most common lesions were neuroendocrine tumor (19.4%), GIST (7.5%) and lymphoma (7.5%).

A study from United States[27] analyzes the impact on incidence and survival rates for SBT after the emergence of CE and deep enteroscopy. In order to assess the potential impact of this technology, they compared

the incidence rates from 1992-2000 and 2001-2009 to determine if there were different diagnostic yields between both periods. SBT remain uncommon in United States, and its incidence significantly increased from 2.5 during the 1992-2000 time frame to 3.1 per 100000/year in the later period of time ($P < 0.004$). The survival was significantly better in the 2001-2009 cohort (52.6% *vs* 63.1% 5-year survival, $P < 0.001$). Stage-specific analysis showed a significant rise in more distant disease only in African-Americans after 2000, which may reflect factors in tumor biology, treatment, and/or access to care of these patients.

In the present study, we reported on 28 patients (4.5%) with MSBTs, all distal to Treitz. When DBE was carried out, there was a suspicion of SBT in all cases. The histological type distribution is quite different between different countries. Adenocarcinoma[3,20,28], neuroendocrine SBT[1,4] and lymphoma[21] have been reported to be the most frequent histological type by different authors. These differences are probably due to the different geographical distributions and clinical presentations of different studies of patient's populations. In our study, GIST was the most common MSBT followed by adenocarcinoma.

DBE allowed histopathological diagnosis in most patients (71.4%), except in GI stromal tumors. The histological detection rate in GIST was low (57.4%) but higher than reported by other authors[22,29]. In addition, there were some extremely rare tumors detected, such as jejunal Kaposi sarcoma.

MSBTs were more common among men (71.4%). These tumors may be presented with complete SB stenosis and/or acute overt OGIB, requiring early management by emergency DBE[30-32] or surgery[33]. This procedure may define the characteristics of SB stenosis or bleeding in order to make a surgery decision and/or perform endoscopic treatment[34,35].

There has been recently reported[5] that in patients presented with OGIB, DBE following a positive CE may be the first option, but direct surgery may also be indicated. Interventional digital subtraction angiography has also been reported to be effective in GIST with bleeding[36].

Among patients with a high clinical suspicion of a SBT in the setting of a negative CE result, radiological imaging or deep enteroscopy are equally indicated. CT scan or MR is the preferred initial test in patients with obstructive symptoms. We have performed a DBE following a positive CE in all cases to have a histological and endoscopic diagnosis.

We are also convinced that the entire exploration of the SB in selected cases such as patients with neuroendocrine tumors may be crucial, because this may impact further management. In our series, we have reported multiple adenocarcinomas or neuroendocrine tumors in the same patient. In addition, the histological analysis may have different diagnostic yields within different lesions of the same MSBT. In other cases, to achieve the primary MSBT location for histological and endoscopic diagnosis may be enough.

Thus, DBE has proven to be accurate in management of MSBT. In our study, DBE modified the outcome of 7 patients (25%), not only because of diagnosis capabilities but also of therapeutics interventions.

However, there were some limitations of our study as the retrospective design and potential referral bias.

In conclusion, DBE is critical in the management of MSBT and may have an impact delaying or avoiding emergency surgery. This procedure clarifies the tumor location and characteristics allowing tattoo injection to guide a possible surgery and provides additional information to other procedures that may be decisive in the clinical course of these patients.

COMMENTS

Background

Malignant small bowel tumors (MSBT) are a heterogeneous group of rare tumors. However, the incidence of these neoplasms is increasing correlated to the expansion of deep enteroscopy and video capsule endoscopy.

Research frontiers

There're different histological subtypes of MSBT with different prognosis and management. The real incidence of each histological type and clinical characteristics are not well-established. Studies to date have reported different distributions of these neoplasms depending on the *geographical area*. Recently, double-balloon enteroscopy (DBE) following capsule endoscopy was confirmed as a valid strategy in patients with a suspected MSBT presenting with obscure gastrointestinal bleeding (OGIB).

Innovations and breakthroughs

Most of studies to date report series from Asia or United States. There're few large European reports of MSBT. In addition, there's no consensus regarding the most common histological type or clinical presentation by different authors. The present study represents a large series of a referral center in DBE. The authors have considered only patients with jejunal of ileal tumors in order to clarify the DBE role in these cases. OGIB was the most common clinical presentation and gastrointestinal stromal tumors the most common type.

Applications

This study clarifies the DBE role in MSBT. The present data might suggest that DBE might impact in about 25% of patients with MSBT by modifying surgery approach.

Terminology

DBE is an endoscopic technique originally described by Yamamoto that allows the entire examination of the small bowel, with two balloons fitted onto the tips of the scope and over tube.

Peer-review

This study clarifies the role of DBE in the management of MSBT on proper scientific level.

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ORIGINAL ARTICLE

Retrospective study

Evaluation of the margins of differentiated early gastric cancer by using conventional endoscopy

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Author contributions: Yoshinaga S performed endoscopic examinations and therapies, and also wrote this manuscript mainly; Oda I, Abe S, Nonaka S, Suzuki H, Takisawa H and Saito Y performed endoscopic examinations and therapies; Taniguchi H evaluated resected specimens pathologically and took pictures of resected specimens.

Ethics approval: We explain all patients about comprehensive prior consent arrangements that we use every data and figures except genetic materials for studies. Therefore, Institutional Review Board of our hospital did not review this study.
Informed consent: All study participants, or their legal guardian agreed to this aforementioned comprehensive prior consent.
Conflict-of-interest: The authors have no conflict of interest directly relevant to the contents of this study.
Data sharing: No additional data are available.

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Abstract

AIM: To evaluate the determination of the margin of differentiated-type early gastric cancers by using conventional endoscopy.

METHODS: We retrospectively evaluated 364 differentiated early gastric cancers that were endoscopically resected as en-bloc specimens and diagnosed pathologically in detail between November 2007 and October 2008. All procedures were done with conventional endoscopes and all endoscopic samples, before and after indigo carmine dye, were re-evaluated using a digital filing system by one endoscopist. We analyzed the incidence of lesions with unclear margins and the relationship between unclear margins and relevant clinicopathological findings.

RESULTS: The rate of lesions with unclear margins was 20.6% (75/364). Multivariate regression analysis suggested that the factors that make the determination of the margin difficult were normal color, presence of components of flat area (0-IIb), a diameter ⩾ 21 mm, ulceration, and components of poorly differentiated adenocarcinoma in the mucosal surface.

CONCLUSION: As many as 20% of differentiated early gastric cancers show unclear margins. Consideration of the factors associated with unclear margins may help endoscopists to accurately determine the margins of the lesion.

Key words: Early gastric cancer; Conventional endoscopy; Determination of the margin

Core tip: As many as 20% of differentiated early gastric cancers show unclear margins by using conventional endoscopy. Consideration of the factors associated with unclear margins, such as normal color, presence of components of flat area (0-IIb), a diameter ⩾ 21 mm, ulceration, and components of poorly differentiated adenocarcinoma in the mucosal surface, may help endoscopists to accurately determine the margins of the lesion.

Yoshinaga S, Oda I, Abe S, Nonaka S, Suzuki H, Takisawa H, Taniguchi H, Saito Y. Evaluation of the margins of differentiated early gastric cancer by using conventional endoscopy. *World J Gastrointest Endosc* 2015; 7(6): 659-664 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i6/659.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i6.659

INTRODUCTION

Since Gotoda *et al*[1] described the incidence of lymph node metastasis from early gastric cancer and with the development of endoscopic submucosal dissection (ESD), early gastric cancer is often resected endoscopically. When endoscopic resection of early gastric cancers is performed, it is important to accurately determine the margin of the lesion. A vague determination of the location of the margin may allow residual cancer to remain, leading to recurrences and additional resections. Recently, imaged enhanced endoscopy (IEE) procedures, such as narrow band imaging (NBI), auto fluorescence imaging (AFI), or flexible spectral imaging color enhancement (FICE) have been developed; however, these methods have not been adopted everywhere. Therefore, an accurate understanding of the use of conventional endoscopes is still relevant.

In this study, we evaluated the determination of the margin of differentiated-type early gastric cancers by using conventional endoscopes and investigated the factors that may make the margin unclear.

MATERIALS AND METHODS

A total of 381 differentiated early gastric cancers were resected endoscopically between November 2007 and October 2008. We excluded 17 early gastric cancers that could not be evaluated in detail because of piecemeal resection, severe burning effects, or other confounding factors. A total of 364 early gastric cancers were included in this study. We reviewed the clinical records, endoscopic images, endoscopy reports, and pathology reports for every patient and analyzed the incidence of lesions with unclear margins and the relationship between unclear margins and the following clinicopathological findings: age, sex, tumor location, tumor color, macroscopic type, component of flat area, tumor size, ulcer finding, component of poorly differentiated adenocarcinoma in the mucosal surface, and intestinal metaplasia around the lesion.

Endoscopic procedure

All patients drank a solution containing 40000 units of pronase (Pronase MS®; Kaken Pharmaceutical Products, Tokyo, Japan), 4 mL of 2% dimethicone (Gascon®; Kissei Pharmaceutical Co., Tokyo, Japan) and 2 g of $NaHCO_3$ to dissolve mucus and bubbles before examination. All procedures were done with conventional endoscopes (GIF-Q240, Q260, H260; Olympus Optical Co., Tokyo, Japan) and without magnifying endoscopy, NBI, or AFI. All endoscopic images were recorded by using a digital filing system (NEXUS; Fuji Film Medical Co., Tokyo, Japan). All endoscopic images before and after indigo carmine dye (0.2%) were reviewed in this study by using a digital filing system by one individual (S.Y) who has 10 years of experience as an endoscopist.

Definitions

Lesions with an unclear margin were defined as lesions with an undelineated margin or an inaccurate marking. An undelineated margin was determined by reviewing the endoscopic images. The identification by the endoscopist of a difference between the lesion and surrounding mucosa in terms of colors, surface morphology, and a height more than two-thirds the size of the circumference was considered a delineated margin (Figure 1). If it was not possible to make a distinction, it was classified as an undelineated margin lesion (Figure 2). We also evaluated the markings made before resection to recognize the tumor margin. We defined an accurate marking if all markings were made outside of the tumor in the resected specimen (Figure 3A). If not, we defined it as an inaccurate marking (Figure 3B). The tumor color and location were also determined endoscopically. The stomach is anatomically divided into three parts: the upper third (U), middle third (M), and lower third (L). The cross-sectional circumference of the stomach is divided into four equal parts; the lesser and greater curvatures, and the anterior and posterior walls based on the Japanese Classification of Gastric Carcinoma[2]. The main macroscopic type of the tumor was classified based on the Paris classification[3], and the components of flat area (0-IIb) of the tumor, tumor size, ulceration findings, components of poorly differentiated adenocarcinoma in the mucosal surface, and metaplasia around the tumor were determined histopathologically.

Statistical analysis

Statistical analysis were made by using the Student's *t* test for evaluating the patients' ages and the tumor sizes, and by using the χ^2 test with Yate's correction and the Fisher exact test for evaluating any other factors.

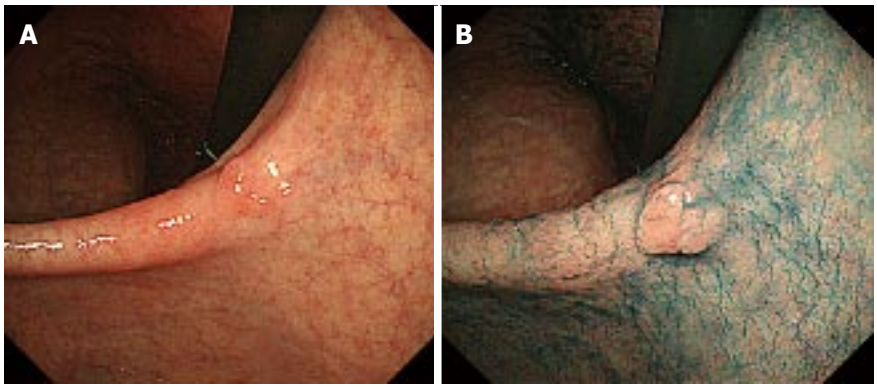

Figure 1 A case of a delineating lesion (0-IIa). Before (A) and after (B) indigo-carmine dye, the margin of the tumor was clear.

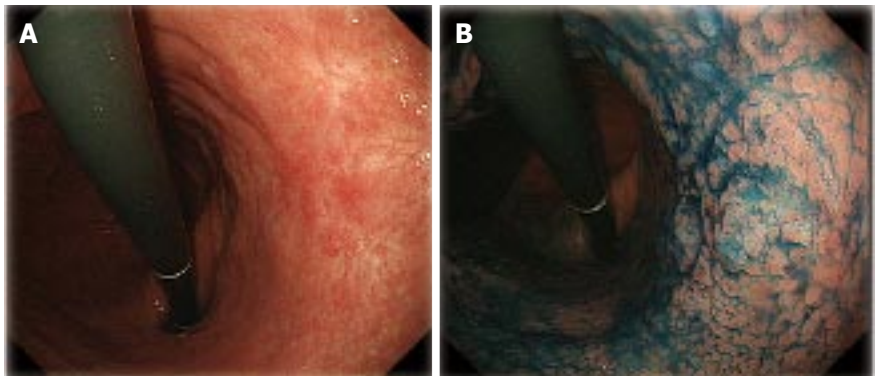

Figure 2 An undelineated margin lesion. A: A case of an undelineating lesion (0-IIc) with ulceration findings; B: After indigo-carmine dye, the margin of the tumor was still unclear.

A level of $P < 0.05$ was considered to be statistically significant. After evaluating the factors that made the determination of the margin difficult, we decided to use logistic regression analysis for further analysis of those factors.

RESULTS

Incidence of lesions with unclear margin

The characteristics of the 364 candidate lesions reviewed during this period are described in Table 1. There were 27 undelineated margin lesions and 337 delineated margin lesions. There were 62 lesions with inaccurate markings and 302 lesions with accurate markings (Table 1). Consequently, 14 lesions were found to have overlapping results. Therefore, there were 75 lesions with unclear margins (Figure 4). The rate of those lesions in this group was 20.6% (75/364).

Factors that made determination of the margin difficult

Factors that had significant correlations with unclear margins were tumor location (three parts), color, components of the flat area (0-IIb), tumor size, ulceration, and components of poorly differentiated adenocarcinoma in the mucosal surface (Table 2). After evaluating those 6 factors by multivariate regression analysis, the factors that made the determination of the margin difficult were normal coloration (OR = 2.095; 95%CI: 1.040-4.217; $P = 0.0383$), components of flat area (0-IIb) (OR = 4.900; 95%CI: 1.610-14.913; $P = 0.0051$), the diameter $\geqslant$ 21 mm (OR = 3.852; 95%CI: 2.165-6.852; $P < 0.0001$), ulceration findings (OR = 2.307; 95%CI: 1.156-4.604; $P = 0.0178$), and components of poorly differentiated adenocarcinoma in the mucosal surface (OR = 6.650; 95%CI: 2.590-17.073; $P < 0.0001$) (Table 3).

DISCUSSION

After ESD was developed, early gastric cancer was often resected endoscopically, especially in Japan. Previously reported[4-6] accuracy rates for the delineation of the margin by using conventional endoscopy were almost 80% to 85%, although the criteria for the determination of the margin were not commonly specified in those reports. In this study, we defined the accuracy rate not only by endoscopic images but also by pathological study of the specimens, and the accuracy rate was almost the same as that shown in previous reports. Asada-Hirayama *et al*[7] reported a similar study to ours, and in their result, the accuracy rate for the delineation of the margin was 92.6%, which was much higher than that seen in previous reports, including our study. However, they evaluated only markings on the resected

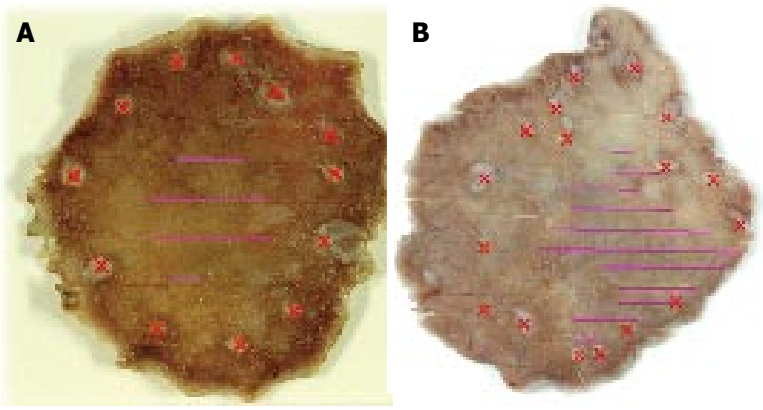

Figure 3 Cases of accurate and inaccurate markings. A: A case of accurate markings. The purple lines indicate the tumor area. The red crosses indicate the marking; B: A case of inaccurate markings. The purple lines indicate the tumor area. The red crosses indicate the marking.

Table 1 The characteristics of 364 lesions

Age (yr)	
Median ± SD	70 ± 9
Range	30-92
Sex	
Men (%)	293 (80.5)
Women (%)	71 (19.5)
Tumor location (three parts)	
U (%)	74 (20.3)
M (%)	144 (39.6)
L (%)	146 (40.1)
Tumor location (cross-sectional parts)	
Less (%)	140 (38.5)
Gre (%)	59 (16.2)
Ant (%)	64 (17.6)
Post (%)	101 (27.7)
Color	
Reddish (%)	213 (58.5)
Discolored (%)	87 (23.9)
Normal color (%)	64 (17.6)
Margin of the lesion	
Delineated	337 (92.6)
Undelineated	27 (7.4)
Main macroscopic type	
0-I (%)	11 (3.0)
0-IIa (%)	154 (42.3)
0-IIb (%)	6 (1.6)
0-IIc (%)	193 (53.0)
Components of flat area (0-IIb)	
Presence (%)	17 (4.7)
Absense (%)	347 (95.3)
Tumor size (mm)	
Median ± SD	16 ± 13
Range	2-100
Ulceration finding	
Presence (%)	62 (17.0)
Absense (%)	302 (83.0)
Components of poorly differentiated adenocarcinoma in the mucosal surface	
Presence (%)	26 (7.1)
Absense (%)	338 (92.9)
Metaplasia around the lesion	
Presence (%)	337 (92.6)
Absense (%)	27 (7.4)
Marking	
Right	302 (83.0)
Wrong	62 (17.0)

SD: Standard deviation; U: The upper third of the stomach; M: The middle third of the stomach; L: The lower third of the stomach; Less: The lesser curvature; Gre: The greater curvatures; Ant: The anterior wall; Post: The posterior wall.

specimens and they used not only conventional endoscopes, but also magnifying endoscopes with NBI. Although there was no significant difference in the accuracy between the 2 kinds of endoscopes in their study, this factor might have influenced the margin delineation rates.

Tanabe *et al*[6] reported the factors that make the delineation of the margin difficult as (1) large lesions (> 31 mm); (2) flat lesions or those with a flat area; (3) adenocarcinoma with low-grade atypia; (4) gastric mucin phenotype (G-type) adenocarcinoma or gastric predominant gastric and intestinal mucin phenotype (G > I-type) adenocarcinoma; and (5) carcinoma cells invading the middle to deeper portion of the mucosa under normal covering epithelium. In our study, 2 factors, lesion size and flat area, were almost the same as the factors that Tanabe *et al*[6] reported, and Asada-Hirayama *et al*[7] reported similar results. To achieve a complete resection, we should observe for those factors that demonstrate a more difficult to differentiate margin, and if the lesion might have such characteristics, we should examine the margin more carefully to ensure an accurate determination. Conventional endoscopy can demonstrate the tumor size and ulceration findings, but sometimes it is difficult to identify components of the flat area. To solve this difficulty, IEE, such as a magnifying endoscope, NBI[8,9], FICE[10], and an acetic acid-indigo carmine mixture (AIM)[11], might be useful. Yao *et al*[8] reported magnifying endoscopy with NBI may allow reliable delineation of the lateral extent of carcinomatous tissue, and in this study, a demarcation line was identified in 97 of 100 carcinomas (97%). Additionally, Nagahama *et al*[9] reported that magnifying endoscopy with NBI could determine margins in 72.6% of the lesions that show unclear margin using conventional endoscopes. AIM was developed by Kawahara *et al*[11] and they reported the diagnostic accuracy of AIM observation was 90.7%. In contrast, the diagnostic accuracy of indigo carmine observation was 75.9% in that study. AIM is also easy to use without special equipment. Kadowaki *et al*[12] mentioned that magnifying endoscopy with NBI and acetic acid is easier compared to other magnifying endoscopy methods to recognize the demarcation of

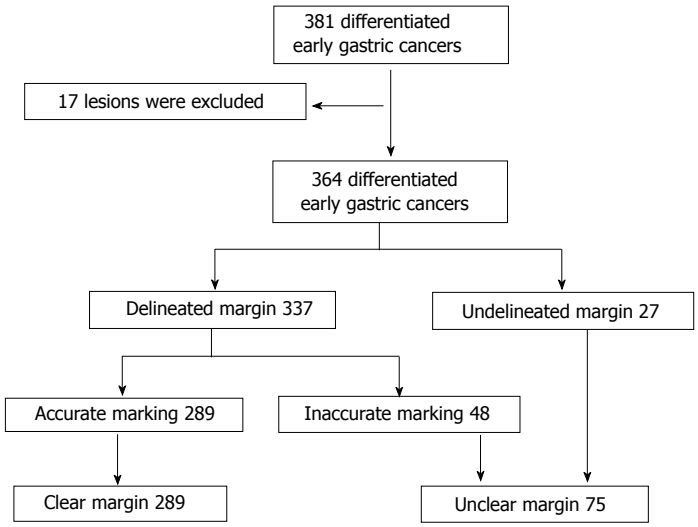

Figure 4 Flow chart of this study.

Table 2 The comparison between "clear margin" and "unclear margin"

	Clear margin (n = 289)	Unclear margin (n = 75)	
Age (yr)			
Median ± SD	70 ± 8	72 ± 10	NS
Range	37-92	30-90	
Sex			
Men (%)	237 (82.0)	56 (74.7)	NS
Women (%)	52 (18.0)	19 (25.3)	
Tumor location (three parts)			
U (%)	54 (18.7)	20 (26.7)	P = 0.0128
M (%)	108 (37.4)	36 (48.0)	
L (%)	127 (43.9)	19 (25.3)	
Tumor location (cross-sectional parts)			
Less (%)	113 (39.1)	27 (36.0)	NS
Gre (%)	47 (16.3)	12 (16.0)	
Ant (%)	51 (17.6)	13 (17.3)	
Post (%)	78 (27.0)	23 (30.7)	
Color			
Reddish (%)	165 (57.1)	48 (64.0)	P = 0.0049
Discolored (%)	79 (27.3)	8 (10.7)	
Norm-colored (%)	45 (15.6)	19 (25.3)	
Main macroscopic type			
0-I (%)	10 (3.5)	1 (1.3)	NS
0-IIa (%)	120 (41.5)	34 (45.3)	
0-IIb (%)	3 (1.0)	3 (4.0)	
0-IIc (%)	156 (54.0)	37 (49.3)	
Components of flat area (0-IIb)			
Presence (%)	7 (2.4)	10 (13.3)	P = 0.0002
Absense (%)	282 (97.6)	65 (86.7)	
Tumor size (mm)			
Median ± SD	15 ± 11	25 ± 17	P < 0.0001
Range	2-68	3-100	
Ulceration finding			
Presence (%)	43 (14.9)	19 (25.3)	P = 0.0319
Absense (%)	246 (85.1)	56 (74.7)	
Components of poorly differentiated adenocarcinoma in the mucosal surface			
Presence (%)	11 (3.8)	15 (20.0)	P < 0.0001
Absense (%)	278 (96.2)	60 (80.0)	
Metaplasia around the lesion			
Presence (%)	266 (92.0)	71 (94.7)	NS
Absense (%)	23 (8.0)	4 (5.3)	

SD: Standard deviation; U: The upper third of the stomach; M: The middle third of the stomach; L: The lower third of the stomach; Less: The lesser curvature; Gre: The greater curvatures; Ant: The anterior wall; Post: The posterior wall; NS: Not significant.

Table 3 The multivariate regression analysis of the factors that make the determination of the margin difficult

Factors	OR	95%CI	P value
Lcation in the U and M parts	1.769	0.940-3.331	NS
Norm-colored	2.095	1.040-4.217	0.0383
Components of flat area (0-IIb)	4.900	1.610-14.913	0.0051
Tumor size ⩾ 21 mm	3.852	2.165-6.852	< 0.0001
Ulceration finding	2.307	1.156-4.604	0.0178
Components of poorly differentiated adenocarcinoma in the mucosal surface	6.65	2.590-17.073	< 0.0001

OR: Odds ratio; NS: Not significant; U: The upper third of the stomach; M: The middle third of the stomach.

early gastric cancers for non-expert endoscopists as well as expert endoscopists. Utilizing these advanced imaging techniques may make it easier and clearer for all endoscopists to recognize the demarcation of early gastric cancers.

Our study had a few limitations. First, we did not compare endoscopic figures with resected specimens in detail, so there was no evidence that the determination of the margin was completely correct. However, in our study, to evaluate the accuracy as precisely as possible, we strictly determined the criteria of "undelineated margin lesions" using not only endoscopic images but also pathological study of the specimens as well as was done in the study of Nagahama *et al*[9]. Second, our study was a retrospective study, and therefore, the individuals who performed the endoscopic resection and those who re-evaluated the lesions were not the same in almost all cases, and the margins that the 2 endoscopists considered were not same. To solve these 2 limitations, future studies could prospectively demarcate the tumor margin to be able to compare it with the endoscopically resected specimens, and the same endoscopists should evaluate the accuracy of the determination.

In conclusion, approximately 20% of differentiated early gastric cancers showed an unclear margin.

Factors such as normal color, components of flat area (0-IIb), diameter ⩾ 21 mm, ulceration findings, and components of poorly differentiated adenocarcinoma in the mucosal surface can make the determination of the margin difficult. During endoscopic resection, endoscopists should carefully evaluate the margin of the lesion while considering the risk factors for unclear margins.

COMMENTS

Background

When endoscopic resection of early gastric cancers is performed, it is important to accurately determine the margin of the lesion. A vague determination of the margin may result in residual cancer cells, which may cause recurrences and require additional resections.

Research frontiers

Recently, imaged enhanced endoscopy (IEE) procedures, such as narrow band imaging (NBI), auto fluorescence imaging (AFI), or flexible spectral imaging color enhancement (FICE) have been developed. Especially, magnifying endoscopy with NBI may allow reliable delineation of the lateral extent of carcinomatous tissue, and it could determine margins in the lesions that show unclear margin using conventional endoscopes. However, these methods have not been adopted everywhere.

Innovations and breakthroughs

In this study, the authors evaluated the determination of the margin of differentiated-type early gastric cancers by using conventional endoscopy. In order to evaluate the accuracy as precisely as possible, the authors more strictly determined the criteria of "undelineated margin lesions" using not only endoscopic images but also pathological study of the specimens than similar studies.

Applications

The result of this study is an important benchmark to evaluate the new modalities describe above. And when these new modalities are not available, the authors should carefully evaluate the margin of the lesion while considering the risk factors for unclear margins.

Terminology

Endoscopic submucosal dissection is a newly developed technique in the field of endoscopic treatment for gastrointestinal neoplasms because of its high rate of *en bloc* resection. IEE is a dye-based or an equipment-based image enhanced technology to increase the contrast of structures, thus making the mucosal topography, morphology and borders of lesions viewable in finer detail. NBI is one of the equipment-based image enhancement technologies, which improves the contrast of the microvascular structure and fine mucosal patterns in the mucosal surface layer using the narrow-band illumination focused two beams of 415 nm and 540 nm. AFI is one of the equipment-based image enhancement technologies based on the detection of natural tissue fluorescence emitted by endogenous molecules such as collagen, flavins, and porphyrins. FICE is one of the equipment-based image enhancement technologies, which enhance images by extracting spectral images at the desired wavelengths by applying signal processing to the white light generally used by endoscope. An acetic acid–indigo carmine mixture is one of the dye-based image enhancement technologies using both acetic acid for color contrast and indigo carmine for shape contrast.

Peer-review

It is a retrospective study and evaluation of various endoscopic criteria for unclear margins in early gastric cancer may not be perfect. Still this study provides useful guide for future prospective studies to define unclear margins in early gastric cancers.

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CASE REPORT

Metallic stent insertion with double-balloon endoscopy for malignant afferent loop obstruction

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Ethics approval: Case reports do not require examination by the Okayama Saiseikai General Hospital Institutional Review Board. Ethical considerations were upheld and patient personal information was protected.
Informed consent: All study participants, or their legal guardian, provided written informed consent prior to study enrollment.
Conflict-of-interest: The authors declare that there are no competing financial or personal relationships with other people or organizations that could inappropriately influence the research.

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Abstract

Progress in double-balloon endoscopy (DBE) has allowed for the diagnosis and treatment of disease in the postoperative bowel. For example, a short DBE, which has a 2.8 mm working channel and 152 cm working length, is useful for endoscopic retrograde cholangiopancreatography in bowel disease patients. However, afferent loop and Roux-limb obstruction, though rare, is caused by postoperative recurrence of biliary tract cancer with intractable complications. Most of the clinical findings involving these complications are relatively nonspecific and include abdominal pain, nausea, vomiting, fever, and obstructive jaundice. Treatments by surgery, percutaneous transhepatic biliary drainage, percutaneous enteral stent insertion, and endoscopic therapy have been reported. The general conditions of patients with these complications are poor due to cancer progression; therefore, a less invasive treatment is better. We report on the usefulness of metallic stent insertion using an overtube for afferent loop and Roux-limb obstruction caused by postoperative recurrence of biliary tract cancer under short DBE in two patients with complexly reconstructed intestines.

Key words: Afferent loop obstruction; Double balloon endoscopy; Overtube; Metallic stent; Biliary tract cancer

Core tip: Malignant afferent loop and Roux-limb obstruction are intractable complications caused by

postoperative recurrence of biliary tract cancer. Metallic stent insertion using an overtube under double-balloon endoscopy is a safe and feasible treatment option in such cases.

Fujii M, Ishiyama S, Saito H, Ito M, Fujiwara A, Niguma T, Yoshioka M, Shiode J. Metallic stent insertion with double-balloon endoscopy for malignant afferent loop obstruction. *World J Gastrointest Endosc* 2015; 7(6): 665-669 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i6/665.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i6.665

INTRODUCTION

Malignant afferent loop obstruction is a potentially life-threatening adverse event of Billroth II gastrectomy and pancreaticoduodenectomy. The occlusion is generally caused by a recurrent tumor, and often presents as chronic, progressive, partial obstruction[1-3]. This type of complication is expected to increase along with therapeutic advances for malignant tumors, thus necessitating the development of safe, effective treatments.

The general condition of patients with malignant afferent loop obstructions is poor due to cancer progression, and thus a less invasive treatment is preferred. Malignant afferent loop obstructions can be treated with surgery, percutaneous transhepatic biliary drainage, percutaneous enteral stent insertion, or endoscopic therapy[4-6]. Endoscopic stents for digestive tract obstruction are a minimally invasive, useful, and safe treatment[7-9]. The primary obstacle for endoscopic stent treatment in postoperative digestive tract obstruction is the difficulty in approaching the obstructing lesion. Of note, there are reports on the use of double-balloon endoscopy (DBE) for complicated postoperative bowel reconstructions[10,11]. Furthermore, a short DBE, which has a 2.8 mm working channel and 152 cm working length, is useful for endoscopic retrograde cholangiopancreatography in these patients[12]. However, because of the large diameter of the system for delivery of metallic stents (MS) indigestive tract obstructions, they cannot be deployed through the narrow working channel of a short DBE. Therefore, new methods are needed to deploy an MS with DBE.

We report on the usefulness of MS insertion using an overtube under a short DBE for afferent loop and Roux-limb obstruction caused by postoperative recurrence of biliary tract cancer in two patients with complexly reconstructed intestines.

CASE REPORT

Case 1

A man in his sixties underwent Roux-en-Y hepaticojejunostomy because of cholangiocarcinoma. Chemotherapy was performed one year later for recurrence of peritoneal dissemination. Two years after chemotherapy, the patient developed a fever and elevated serum transaminase levels. Laboratory tests were as follows: white blood cell (WBC) counts, 9410/μL (normal: 4500-8500/μL); C-reactive protein, 4.7 mg/dL (normal: < 0.26 mg/dL); total bilirubin, 1.2 mg/dL (normal: 0.2-1.2 mg/dL); γ-glutamyltranspeptidase (γGTP), 256 IU/L (normal: 5-40 IU/L); aspartate aminotransferase (AST), 38 IU/L (normal: 10-35 IU/L); and alanine aminotransferase (ALT), 17 IU/L (normal: 7-42 IU/L). Abdominal computed tomography (CT) showed the reconstructed jejunum that was expanded at the site of hepatectomy, mild expansion of the intrahepatic bile ducts and stenosis of the reconstructed jejunum (Figure 1A). The patient was diagnosed with malignant Roux-limb obstruction due to peritoneal dissemination and cholangitis.

Ultrasound-guided drainage was performed for the dilated jejunal Roux-limb, but repeated inflammatory aggravation with drain obstruction occurred. Therefore, a short DBE was performed with the patient under conscious sedation. The short DBE (EC-450BI5; Fujifilm, Tokyo, Japan) was inserted into the Roux-limb obstruction (Figure 1B), and a 0.035 inch guide-wire (Radifocus; Terumo, Tokyo, Japan) was passed through the site of the stricture. Then, a standard endoscopic retrograde cholangiopancreatography injection catheter (MTW Endoskopie, Düsseldorf, Germany) was inserted, and passage through the stenosis was confirmed by radiography. The guide-wire was exchanged with a 0.035 inch Jagwire (Boston Scientific Co., Natick, MA, United States), and an overtube was left to prevent bowel expansion. The DBE was then removed. Finally, an MS (2.2 cm × 6.0 cm, Wallflex duodenal stent; Boston Scientific Co.) was inserted through the overtube in combination with an over-the-wire technique (Figure 1C) and deployed (Figure 1D). There were no perioperative or postoperative adverse events.

After stent insertion, the patient's cholangitis, general condition, and laboratory tests improved as follows: WBC count, 7960/μL; C-reactive protein, 1.86 mg/dL; total bilirubin, 0.7 mg/dL; γGTP, 96 IU/L; AST, 25 IU/L; and ALT, 19 IU/L. On CT, dilation of the Roux-limb disappeared, and chemotherapy resumed. However, this patient died because of peritonitis carcinomatosa 141 d after stent insertion.

Case 2

A man in his sixties underwent pancreaticoduodenectomy because of Vater's papilla cancer. He developed a fever and jaundice approximately 10 mo after the operation. Laboratory tests were as follows: total bilirubin 9.9 mg/dL; γGTP, 401 IU/L; AST, 273 IU/L; and ALT, 283 IU/L. Abdominal CT showed ascites, dilation of the afferent loop, and a surrounding soft density (Figure 2A). The patient was thus diagnosed with malignant afferent loop obstruction due to peritoneal dissemination and cholangitis.

A short DBE (EC-450BI5; Fujifilm) was performed,

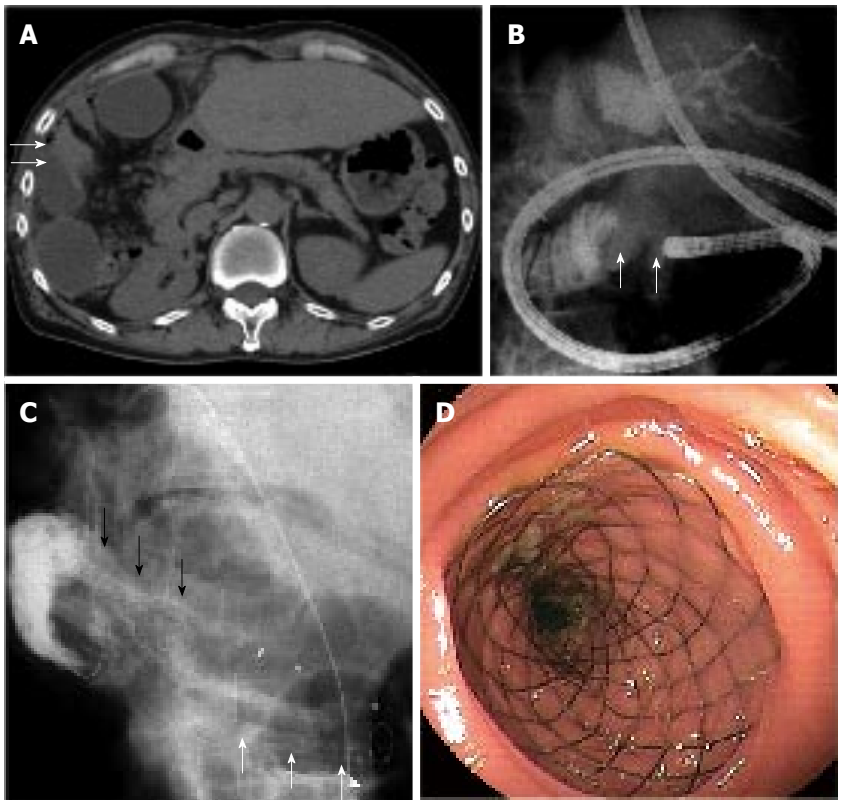

Figure 1 Metallic stent insertion with double-balloon endoscopy for malignant afferent loop obstruction in case 1. A: Abdominal computed tomography showed the reconstructed jejunum that was expanded at the site of hepatectomy, expansion of intrahepatic bile ducts, and the stenosis of the reconstructed jejunum (arrows); B: The stenosis (arrows) was seen when the double-balloon endoscopy (DBE) reached the Roux-limb obstruction; C: An overtube was left to prevent bowel expansion. The DBE was then removed and an metallic stent (MS) (black arrows) was inserted through the overtube (white arrows) in combination with the over-the-wire technique; D: A Wallflex duodenal MS with a diameter of 2.2 cm and a length of 6.0 cm was deployed.

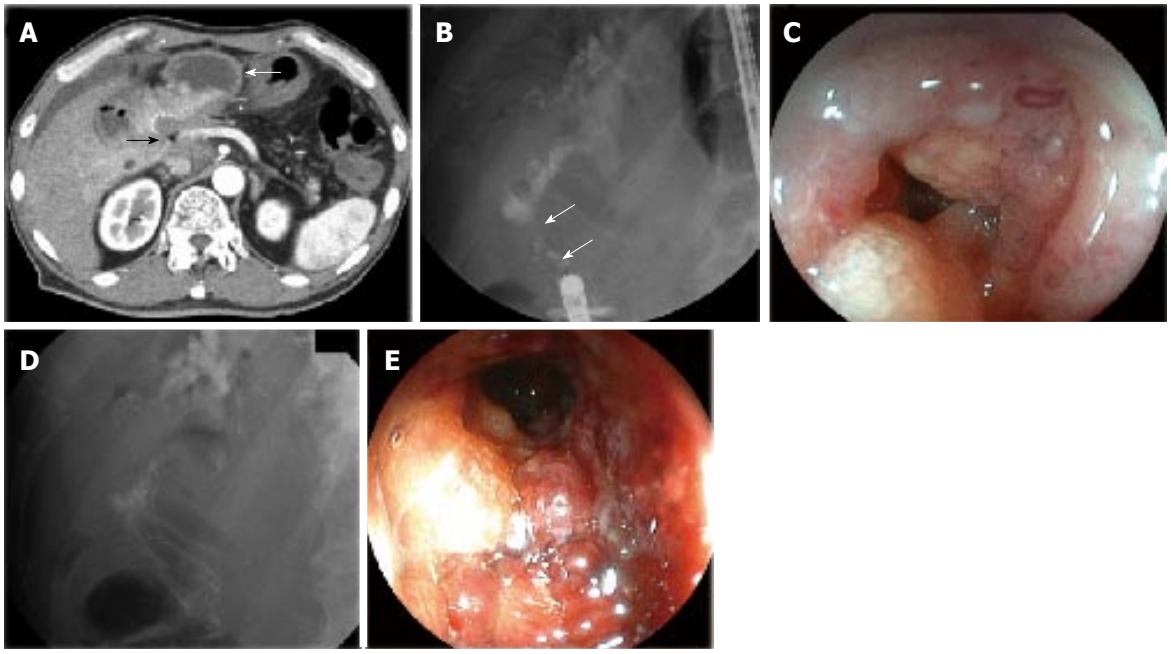

Figure 2 Metallic stent insertion with double-balloon endoscopy for malignant afferent loop obstruction in case 2. A: Computed tomography showed ascites, dilation of the afferent loop (white arrow), and a surrounding soft density (black arrow); B: The double-balloon endoscopy reached the afferent loop obstruction (arrows); C: Stenosis with irregular mucosa was seen; D and E: A Niti-S duodenal metallic stent with a diameter of 2.2 cm and a length of 6.0 cm was inserted and deployed.

which revealed stenosis with irregular mucosa at the afferent loop obstruction (Figure 2B and C). An MS (2.2 cm × 6.0 cm, Niti-S D-type stent; Taewoong Medical Inc., Seoul, South Korea) was inserted and deployed as

described in case 1 (Figure 2D and E). There were no perioperative or postoperative adverse events.

After insertion of the MS, the patient's general condition and laboratory tests improved: total bilirubin, 1.5 mg/dL; γGTP, 296 IU/L; AST, 92 IU/L; and ALT, 77 IU/L. Chemotherapy was resumed, however this patient also died from peritonitis carcinomatosa 140 d after stent insertion.

DISCUSSION

Afferent loop and Roux-limb obstruction are rare adverse events that result in the obstruction of the postoperative intestinal tract. When jaundice and/or fever occur in a postoperative cancer patient with intestinal tract reconstruction, it is important to consider afferent loop or Roux-limb obstruction due to recurrence. Obstructions are typically treated with surgery; however, the general condition of many of these patients is so poor that surgery is not possible. In such cases, insertion of an MS through the stenosis is a useful treatment.

Although percutaneous stent deployment has been reported[13,14], the endoscopic approach allows for direct identification of the stenosis. There are few reports using this method, due to the difficulty in reaching the stenosis with an endoscope, and the need for a scope with a large enough working channel diameter to permit insertion of an MS. In the cases reported here, malignant afferent loop and Roux-limb obstructions were confirmed by DBE and the stenoses were penetrated with a guide-wire. The endoscope was then removed, leaving the overtube to prevent bowel expansion and deploy the MS with an over-the-wire technique. With this method, the stents were safely and easily inserted through the stenoses using a DBE, eliminating the need for a new endoscope. DBE was chosen over a colonoscope in these cases, as it can cause patient discomfort and poses a risk to the patient's health. Stents were safely inserted without a high degree of difficulty and did not produce major adverse events. Moreover, the patients were able to leave the hospital early.

There are other treatments for afferent loop obstruction, such as percutaneous transhepatic biliary drainage or endoscopic ultrasound-guided transhepatic drainage. When a hepatic-jejunal anastomotic stricture coexists, these methods may be particularly useful. However, biliary access can be challenging in patients without dilation of intrahepatic biliary ducts or in patients with ascites. In our cases, we could confirm the absence of judge hepatic-jejunal anastomotic strictures because the bile ducts were easily contrasted by cystography from the afferent loop. Thus, treatments should be selected depending on the patient's condition.

In conclusion, MS insertion using an overtube for afferent loop and Roux-limb obstruction from postoperative recurrence of biliary tract cancer under short DBE is safe and feasible. However, it is necessary to accumulate more cases to determine the true rates of adverse events and confirm the effectiveness of this approach in comparison with surgery and other treatments.

COMMENTS

Case characteristics

Two men in their sixties who underwent Roux-en-Y hepaticojejunostomy after presenting with cholangiocarcinoma and a fever (Case 1) and pancreaticoduodenectomy due to Vater's papilla cancer after presenting with fever and jaundice (Case 2) are reported here.

Clinical diagnosis

Case 1: Fever; Case 2: Fever and jaundice upon physical exam.

Differential diagnosis

Pseudocyst; ileus.

Laboratory diagnosis

Case 1: WBC, 9410/μL; C-reactive protein, 4.7 mg/dL; total bilirubin, 1.2 and 9.9 mg/dL; γ-glutamyltranspeptidase, 256 and 401 IU/L; aspartate aminotransferase, 38 and 273IU/L; and alanine aminotransferase,17 and 283 IU/L, for case 1 and case 2, respectively.

Imaging diagnosis

Computed tomography (CT) in case 1 revealed expansion at the site of hepatectomy in the reconstructed jejunum, mild expansion of intrahepatic bile ducts, and stenosis of reconstructed jejunum; in case 2, CT revealed ascites, dilation of the afferent loop, and a surrounding soft density.

Treatment

Metallic stent insertion with double-balloon endoscopy for malignant afferent loop and Roux-limb obstruction.

Related reports

Afferent loop and Roux-limb obstructions caused by postoperative recurrence of biliary tract cancer are rare and intractable.

Term explanation

Malignant afferent loop obstructions are rare adverse events due to the obstruction of the postoperative intestinal tract of Billroth II gastrectomy and pancreaticoduodenectomy.

Experiences and lessons

Metallic stent insertion using an overtube for afferent loop and Roux-limb obstruction caused by postoperative recurrence of biliary tract cancer under short double-balloon endoscopy is safe and feasible.

Peer-review

The technique is interesting and clinically relevant, and will be of interest to this journal's readership.

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